Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2003-10

Famoxadone/Tanos 50DF

The active ingredient famoxadone and associated end-use product Tanos 50DF Fungicide, containing famoxadone and the currently registered fungicide cymoxanil, for the control of early and late blight in or on potatoes and field tomatoes have been granted temporary registration under section 17 of the Pest Control Products (PCP) Regulations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Famoxadone Technical and fungicide and associated end-use product (EP), Tanos 50DF, containing famoxadone and the currently registered fungicide cymoxanil, developed by DuPont Canada for the control of various fungal diseases on field tomatoes and potatoes. These products were reviewed jointly within the North American Free Trade Agreement's Technical Working Group on Pesticides (NAFTA TWG) Joint Review Program by Health Canada's Pest Management Regulatory Agency and the United States Environmental Protection Agency (USEPA).

Methods for analysing famoxadone in environmental media are available to research and monitoring agencies upon request to the PMRA.

DuPont will be carrying out additional studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document (PRDD) and request comments from interested parties before proceeding with a final regulatory decision.

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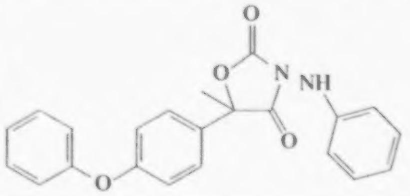
1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Table 1.1.1 Technical Grade Active Ingredient (TGAI) Identification

Active substance:	Famoxadone
Function:	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry	3-anilino-5-methyl-5-(4-phenoxyphenyl)-1,3-oxazolidine-2,4-dione
2. Chemical Abstracts Service (CAS)	5-methyl-5-(4-phenoxyphenyl)-3-(phenylamino)-2,4-oxazolidinedione
CAS number	131807-57-3
Molecular formula	$C_{22}H_{18}N_2O_4$
Molecular weight	374.4
Structural formula	
Nominal purity of active substance	97.8%
Identity of relevant impurities of toxicological, environmental, or other significance	The technical grade Famoxadone does not contain any impurity or microcontaminant known to be a Toxic Substances Management Policy (TSMP) Track-1 substance.

1.2 Physical and chemical properties

Table 1.2.1 Technical product: Famoxadone

Property	Result	Comment
Colour and physical state	Pale cream powder	
Odour	Similar to burnt plastic and vanilla	
Melting point or range	140.3 – 141.8°C	
Boiling point or range	Not applicable	
Specific Gravity	1.31	
Vapour pressure at 20°C	6.4×10^{-7} Pa m^3 mol^{-1}	Not likely to volatilize from water and moist soil surfaces
Henry's law constant at 20°C	4.6×10^{-3} Pa m^3 mol^{-1}	
Ultraviolet (UV) – visible spectrum	λmax = 231 nm **pH** **log ε** acid 4.36 neutral 4.34 basic 4.34 The representative spectra do not show absorbance at above 350 nm.	Not likely to undergo phototransformation
Solubility in water at 20°C	**pH** **Solubility (μg/L)** unbuffered 52 ± 4 2 143 ± 96 3 191 ± 114 5 243 ± 271 7 111 ± 89 9 38 ± 16	Sparingly soluble to insoluble in water

Property	Result	Comment
Solubility (g/L) in organic solvents at 20°C	**Solvent** **Solubility (g/L)** acetone 274 acetonitrile 125 dichloromethane 239 ethyl acetate 125 hexane 0.0476 methanol 10.0 1-octanol 1.87 toluene 13.3	
n-Octanol–water partition coefficient (K_{ow})	**pH** **log K_{ow}** 3.0 4.59 5.0 4.80 7.0 4.65 9.0 5.55	Potential for bioaccumulation
Dissociation constant (pK_a)	Expected to be weakly basic. The dissociation constant could not be measured nor inferred from solubility or octanol–water partition coefficient.	
Stability (temperature, metal)	The product is compatible with aluminum or iron metal and stable when exposed to ferric chloride, in the dark.	

Table 1.2.2 End-use product (EP): Tanos 50 DF

Property	Result
Colour	Brown
Odour	Sweet
Physical state	Solid granule
Formulation type	Wettable granule
Guarantee	25% famoxadone (nominal)
Formulants	The product does not contain any USEPA List 1 formulant nor any formulant known to be a TSMP Track-1 substance.
Container material and description	Plastic

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Solubility in water at 20°C	**pH** **Solubility (μg/L)** unbuffered 52 ± 4 2 143 ± 96 3 191 ± 114 5 243 ± 271 7 111 ± 89 9 38 ± 16	Sparingly soluble to insoluble in water

Property	Result	Comment
Solubility (g/L) in organic solvents at 20°C	**Solvent** — **Solubility (g/L)** acetone — 274 acetonitrile — 125 dichloromethane — 239 ethyl acetate — 125 hexane — 0.0476 methanol — 10.0 1-octanol — 1.87 toluene — 13.3	
n-Octanol–water partition coefficient (K_{ow})	**pH** — **log K_{ow}** 3.0 — 4.59 5.0 — 4.80 7.0 — 4.65 9.0 — 5.55	Potential for bioaccumulation
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Formulants	The product does not contain any USEPA List 1 formulant nor any formulant known to be a TSMP Track-1 substance.
Container material and description	Plastic

Property	Result
Bulk density	0.58 g/mL
pH of 1% dispersion in water	6.5
Oxidizing or reducing action	Not an oxidizer or reducer
Storage stability	No significant change in the level of active substance, nor in the container, was observed after two years' storage in the commercial container, under ambient warehouse conditions.
Explodability	Not explosive by impact, nor thermally sensitive

1.3 Details of uses and further information (OECD 2.1.3)

Tanos 50DF is a dry flowable fungicide, containing 25% famoxadone and 25% cymoxanil, which belong to the fungicide groups 11 and 27 respectively. Tanos 50DF is recommended for use as a preventative fungicide for control of late blight and early blight on potatoes and field tomatoes. It can be applied at 560 to 840 grams product per hectare at seven day intervals with a maximum of six applications per year. Use the higher rate under moderate to high disease pressure. For resistance management it is recommended to alternate with a fungicide having a different mode of action, other than group 11 or 27, after each application of Tanos 50DF.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

A reversed phase High Pressure Liquid Chromatography (HPLC)/UV method was provided for the determination of the active, famoxadone, in the technical product. Based on the validation data and the chromatograms provided, the method was assessed to be sufficiently specific, precise and accurate.

2.2 Analytical methods for formulation analysis

A reversed phase HPLC/UV method was provided for simultaneous determination of famoxadone and cymoxanil present in Tanos 50 DF. Based on the validation data and the chromatograms provided, the method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

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Bulk density	0.58 g/mL
pH of 1% dispersion in water	6.5
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A reversed phase HPLC/UV method was provided for simultaneous determination of famoxadone and cymoxanil present in Tanos 50 DF. Based on the validation data and the chromatograms provided, the method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

2.3 Methods for residue analysis.

2.3.1 Method for environmental residue analysis

2.3.1.1 Analytical Methodology (parent compound and transformation products)—Soil

An HPLC/Mass Spectrometry (MS) method was submitted for the determination of the parent compound, famoxadone and its major transformation products IN-JS940 and IN-KZ007 in soil, sediment and water. A Gas Chromatography (GC) method was submitted for the determination of the parent compound, famoxadone, only. Based on the validation data and the chromatograms provided, the methods were assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

2.3.1.2 Analytical Methodology (parent compound and transformation products)—Sediment

An HPLC/MS method was submitted for the determination of the parent compound and its major transformation products in sediment. Based on the validation data and the chromatograms provided, the methods were assessed to be sufficiently sensitive, precise, accurate and specific for the determination. This HPLC/MS method was also validated for soil and water.

2.3.1.3 Analytical Methodology (parent compound and transformation products)—Water

A GC/Electron-capture Detector (ECD) method was provided for the determination of the parent compound in drinking water ground water and surface water. The HPLC/MS method for sediment was also used for the determination of the parent compound, famoxadone and its major transformation products IN-JS940 and IN-KZ007 in drinking water, ground water and surface water. Based on the validation data and chromatograms provided, the methods were assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

2.3.1.4 Analytical Methodology (parent compound and transformation products)—Biota

An HPLC/UV analytical method was provided for the determination of parent compound in a range of crops. A second HPLC/UV method was provided for the determination of the parent compound in bovine tissues and other animal substrates. These methods were extended to environmental plant and animal matrices.

2.3.2 Multiresidue methods for residue analysis

Famoxadone was screened through multiresidue methods listed in Pesticide Analytical Manual Volume I (PAM Vol. I), Third Edition (January 1994), using Protocols C to E. Protocols A and B were not used because famoxadone does not have an n-methyl carbamate structure (Protocol A), nor is it an acid or phenol (Protocol B). Protocol C showed good analytical response using the ECD and nitrogen-phosphorus detector (NPD). Good recoveries were obtained for the analysis of wine, grapes and tomatoes (92–138%) using Protocol D. Grapes (red seedless) can be analyzed for famoxadone residues using Protocol E involving extraction with the mixed ether elution system, resulting in recovery values of 92 to 108%.

2.3.3 Methods for residue analysis of plants and plant products

An analytical method (AMR 3705-95) was developed for data-gathering and enforcement purposes to quantitate famoxadone in plant matrices. The principle of the method was homogenization/extraction of sample matrices with aqueous acetonitrile, clean-up by solvent partitioning into hexane followed by passage through a Florisil column or various solid-phase extraction (SPE) cartridges and analysis/quantitation by GC-NPD or column switching HPLC-UV (tomato paste). The enforcement methods for plant matrices have undergone adequate independent laboratory validation (ILV). The limit of quantitation (LOQ) was reported to be 0.02 ppm for grapes, tomatoes, barley and wheat grain and 0.05 ppm for barley/wheat straw and green forage. The method/detector response was linear ($r > 0.999$) within the range of 0.01–3.0 μg/mL. Recovery percentages ranged from 73 to 112% (standard deviation (SD) ± 15%) for grapes, tomatoes, grain and straw over a spiking range of 0.02–15 ppm. Confirmation was provided by HPLC-MS, GC-MS or GC-MS/MS. The method was adequately radiovalidated using bioincurred residues from plant metabolism studies. Several analytical methods were developed to quantitate residues of famoxadone in plant matrices and modifications were incorporated (extraction solvent, clean-up steps) in order to minimize the fats, oils, polar and non-polar co-extracted interferences, depending on the matrices. These variations are not expected to affect the extraction profile and efficiency. These analytical methods are considered acceptable for purposes of data collection.

2.3.4 Methods for residue analysis of food of animal origin

Two analytical methods were developed for the analysis of famoxadone residues in livestock commodities for data gathering and enforcement purposes. An analytical method (AMR 3750-96) was developed and validated for the quantitation of famoxadone in/on milk, eggs and animal tissues by gas-liquid chromatography (GLC) using a nitrogen-phosphorus detector (GLC-NPD). The principle of this method included homogenization/extraction of sample matrices with aqueous acetonitrile, salting out of the aqueous acetonitrile sample extract and clean-up by hexane solvent partitioning and Florisil column. Recoveries ranged from 76 to 120% (± 13%) The LOQ reported was 0.02 ppm for all bovine and poultry tissues, eggs and milk, except for cream (0.1 ppm).

A second method (DuPont-1452), was used to extract famoxadone residues from milk and tissue samples by Matrix Solid Phase Dispersion (MSPD), using octadecylsilyl-derivatized packing as a support and acetonitrile as an eluent. Samples were cleaned up by solid-phase extraction using disposable alumina, carbon and silica solid phase extraction cartridges prior to quantitation by LC with column switching and UV detection. Recoveries ranged from 71 to 113% (± 13%). The method limit of detection (LOD) is reported to be 0.007 ppm and the method limits of quantitation (LOQ) are 0.01 ppm for milk, kidney, muscle, fat and cream, and 0.05 ppm for liver.

Both methods were found to give acceptable recoveries for the analysis of famoxadone in animal matrices and milk. Good linearity (correlation coefficient, $r = 0.999$) was observed in the range of 0.007 to 0.12 ppm (DuPont-1452) and 0.02 to 3 ppm (AMR 3750-96) for the analysis of famoxadone. Representative chromatograms of control samples showed no interferences from animal matrix components, reagents, solvents or glassware. Method AMR 3750-96 was not radiovalidated. Method DuPont-1452 was adequately radiovalidated using samples from the goat metabolism study. Neither method has undergone an independent laboratory validation. These analytical methods are considered acceptable for data gathering. However, DuPont-1452 is the preferred method for enforcement purposes.

3.0 Impact on human and animal health

3.1 Integrated Toxicological Summary

A detailed review of the toxicology database available for famoxadone has been completed. Data submitted were complete and comprehensive and included the full battery of studies currently required for registration purposes. Studies were conducted in conformance with currently acceptable international testing protocols. The scientific and regulatory quality of the toxicology data base is considered sufficient to generally define the toxicity of this chemical.

In both rats and dogs, famoxadone was rapidly absorbed from the G.I. tract, but absorption appeared to be limited (<40%). There was no indication of ^{14}C-residues accumulating in tissues. The relative distribution of radioactivity between tissues was similar regardless of sex and dose level. Approximately 90% of the administered radioactivity was recovered in the fecal excreta. Urinary elimination was limited and accounted for <10% of the administered dose. The pattern of excretion, distribution and metabolism was similar regardless of sex, ^{14}C-label position, dose level and pretreatment. In both rats and dogs, the highest concentration of the radioactivity was found in the liver and fat. In dogs, the high concentration of radioactivity was also recorded in eyes, plasma, red blood cells and aqueous humor. Unmetabolised famoxadone was the major component recovered in the feces. Hydroxylated metabolites (IN-KZ007 and IN-KZ534) were also identified in the feces. No parent compound was detected in the urine. Minor amounts of hydrolytic (IN-JL856) and hydrolysis cleavage products (IN-KZ000 and IN-BY759, 4-acetoxyaniline) were detected in the urine.

Technical famoxadone appeared to be of low oral, dermal and inhalation toxicity. The product is minimally irritating to eyes and slightly irritating to skin. According to the Buehler test in guinea pigs, the test material is not a skin sensitizer.

DPX-KP481-25 50WG (EP) appeared to be of moderate acute oral toxicity, low dermal and inhalation toxicity. The product is mildly irritating to eyes and minimally irritating to skin. According to the Buehler test in guinea pigs, the test material is not skin a sensitizer.

In subchronic and chronic repeat dosing studies in mice, rats and dogs, the most common indicators of toxicity were hepatotoxicity and hematological changes consistent with anemia. Rats and dogs displayed similar sensitivity to famoxadone, while mice were less sensitive. Regenerative anemia was evidenced by reticulocytosis, increased means cell volume, extramedullary hematopoiesis and mild bone marrow hyperplasia. In dogs, in addition to hepatotoxicity and hemolytic anemia, famoxadone-induced treatment-related cataracts in the lens and microscopic lens lesions consisting of a small focal zone of swollen lens fibre of the posterior lens capsule. The eye effects in dogs were observed at dose levels below those at which any other effect was observed in other species. The no observed adverse effect level (NOAEL) for males in a 13-week dog study is 1.3 mg/kg bw/day, based on increased incidence of lenticular cataracts and microscopic lens lesions at a dose level of 10.0 mg/kg bw/day. The NOAEL for females could not be ascertained because of microscopic lens lesion observed in one dog at the lowest dose tested. The lowest observed adverse effect level (LOAEL) for females is 1.4 mg/kg bw/day. Also in a 1-year dog study, the NOAEL was not determined due to a serious fixation artifact that affected all sections examined such that only prominent lens degeneration was detectable, and as a consequence, a no effect level could not be reliably determined.

In the mouse carcinogenicity study, the NOAEL of 96 mg/kg bw/day was set based on the slight hepatotoxicity (focal necrosis, diffuse fatty changes, liver discolouration, Kupffer cell lipofuscin, amyloidosis and apoptosis).

In the rat chronic/oncogenicity study, the female rats appeared to be more sensitive than males. The NOAEL of 2.2 mg/kg bw/day was set for females and 8.4 mg/kg bw/day for males based on decreased body-weight gain (bwg), slight hemolytic anemia and slight hepatotoxicty.

In a 1-year gavage study in monkeys, the NOAEL was set at 100 mg/kg bw/day based on mild hemolytic anemia at the highest dose level of 1000 mg/kg bw/day.

In carcinogenicity studies in male and female rats and mice, famoxadone did not demonstrate any evidence of carcinogenic potential.

Genotoxicity studies indicated that famoxadone was negative for induction of mutation in bacterial and mammalian cell in vitro. It was positive when tested for production of chromosome aberrations in mammalian cells in vitro but was negative for clastogenicity and aneuploidy in vivo in the mouse micronucleous assay. Famoxadone did not produce unscheduled DNA synthesis (UDS), either in vitro or in vivo. Based on the weight of evidence, famoxadone is not considered mutagenic.

There was no evidence of teratogenicity in the developmental toxicity studies, nor was there any evidence of increased susceptibility of the young. As in the subchronic toxicity studies, general toxicity was observed in the dams as decreased body weight (bw), bwg and food consumption. In rats, no developmental effect was observed at the highest dose level of 1000 mg/kg bw/day (limit dose). In rabbits, both maternal and developmental NOAELs were set at 350 mg/kg bw/day. This was based on the increased abortion rate and decreased bwg and food consumption in dams. Since it cannot be determined whether the abortions were due to maternal or developmental toxicity (or both), these abortions are considered to be a treatment-related developmental effect.

Famoxadone was not a reproductive toxicant and there was no qualitative or quantitative evidence of increased susceptibility in offspring in the 2-generation reproductive toxicity study. The NOAEL for reproductive effects was set at the highest dose of 45 mg/kg bw/day. The parental NOAEL was 11.3 mg/kg bw/day, based on decreased bw and hepatotoxicity (effect on the liver enzymes and microscopic changes including liver foci, discolouration, focal fatty changes, eosiniphilic focus and cellular alteration). The offspring NOAEL was also 11.3 mg/kg bw/day, based on decreased pup body weights.

The evidence of neurotoxicity observed in the acute neurotoxicity study in rats is equivocal. Increased evidence of palpebral (eyelid) closure observed only in males and only on day 1 may suggest a slight neurotoxic effect at the limit dose of 2000 mg/kg bw/day.

Of considerably more concern were the clinical observations in the 13-week feeding study in dogs of continuous myotonic twitching in the high-dose males and females (23 mg/kg bw/day) that were first observed approximately 4 hours after feeding on day 21 and thereafter were regularly observed (particularly after feeding) throughout entire remaining duration of the study. In addition, one female dog in this high-dose group also had convulsion and ataxia on day 34.

There was no evidence of neurotoxicity in other toxicity studies with famoxadone. The NOAEL subchronic neurotoxicity in rats is 47 mg/kg bw/day (the highest dose tested).

In a 28-day immunotoxicity study, famoxadone did not produce treatment-related effects on any of the immune parameters examined, in either rats or mice, at dose levels up to and including 55 mg/kg bw/day in rats and 1190 mg/kg bw/day in mice.

3.2 Toxicological endpoint for assessment of risk following long-term exposure—Acceptable Daily Intake (ADI)

The recommended ADI for famoxadone is 0.0014 mg/kg bw/day. The most appropriate study for selection of toxicity endpoints for chronic dietary exposure was a 90-day toxicity study in dogs, with a LOAEL of 1.4 mg/kg bw/day. This was based on the treatment-related eye lesions (cataract). A total uncertainty factor (UF) of 1000 is required to account for standard uncertainty factors of 10× for inter-species extrapolation, 10× for intra-species variability and an additional uncertainty factor of 10× for the use of the LOAEL from the subchronic study for the chronic scenario.

$$\mathbf{ADI = \frac{LOAEL}{UF} = \frac{1.4\ mg/kg\ bw/day}{1000} = 0.0014\ mg/kg\ bw/day}$$

This ADI provides a margin of safety (MOS) equal to 7, which is 142 times the NOAEL for the neurological endpoint (NOAEL = 10.0 mg/kg bw/day in the 90-day dog study) and 250 000 times the MOS for the developmental study in rabbits (NOAEL=350 mg/kg bw/day).

A 1-year feeding study in dogs is also available but it was not selected as the basis for the ADI; because of a serious fixation artifact that affected all sections examined such that only prominent degeneration was detectable, a NOAEL could not be reliably determined.

3.3 Toxicological endpoint for assessment of risk following acute dietary exposure—Acute Reference Dose (ARfD)

No toxicological endpoint attributable to a single oral dose was identified in the available toxicity studies on famoxadone that would be attributable to females (13–50 years) or to the general population (including infants and children).

In an acute neurotoxicity study in rats, an increased incidence of palpebral (eyelid) closure was observed only in male rats and only on day 1 of dosing at the limit dose of 2000 mg/kg bw/day. This effect, although treatment-related, is not considered to be of sufficient toxicological concern to be the basis for establishment of an ARfD. No treatment-related effect was observed in female rats in this study at the limit dose of 2000 mg/kg bw/day.

In a developmental toxicity study in rabbits, 4 of 17 does aborted between the gestation days 19 and 23. Markedly decreased bw, bwg and food consumption were observed in these dams. Because all abortions occurred late in the study and only after the full treatment period ended, these abortions, although treatment-related, are considered to result most likely from multiple exposures to the test material, rather than to a single exposure and therefore are not appropriate endpoints for an ARfD.

3.4 Toxicological endpoint for assessment of occupational and bystander risks—Acceptable Operator Exposure Level/Margin of Exposure (AOEL/MOE)

For short- and intermediate-term occupational exposure via the dermal and inhalation routes, the 13-week dog toxicity study was considered most appropriate.

Short-term occupational dermal exposure (1–30 days)
The endpoint for short-term dermal exposure is based on a NOAEL of 10 mg/kg bw/day. At the next highest dose of 24 and 23 mg/kg bw/day (M/F), treatment-related myotonic twitches were observed in both sexes starting on day 21. A 28-day dermal study in rats is available, but not used as the basis for the short-term dermal risk assessment because the NOAEL in this study is 250 mg/kg bw/day and does not protect the effects observed in all the available studies for this short-term time frame. The target MOE for this scenario is 100 (10× for intraspecies extrapolation and 10× for intraspecies variation). No additional safety factor is required because the proposed dose is a NOAEL for an effect (myotonic twitches) that occurred within the first 30 days of the study.

Intermediate-term occupational dermal exposure (1–6 months)
The endpoint for intermediate-term dermal exposure is a LOAEL of 1.4 mg/kg bw/day based on treatment-related microscopic lens lesions (cataracts) observed in eyes of female dogs at 13 weeks. The NOAEL could not be determined because 1.4 mg/kg bw was the lowest dose tested in the female dogs in this study. No dermal study with a duration of greater than 28 days is available. The study and endpoint selected for this risk assessment provide protection from the effects observed in all the available studies for this intermediate-term time frame. The target MOE is 300 (10× for intraspecies extrapolation, 10× for intraspecies variation and 3× because a LOAEL was used).

Short-term inhalation occupational exposure (1–30 days)
The endpoint for short-term inhalation exposure is based on a NOAEL of 10 mg/kg bw/day. At the next highest dose of 24 and 23 mg/kg bw/day (M and F), treatment-related myotonic twitches were observed in both sexes starting on day 21. There is no inhalation study of any duration (other than acute studies) available for famoxadone. The study and endpoint selected for this short-term inhalation risk assessment are based on an oral study with a proposed dose of 10 mg/kg bw/day and provide protection from the effects observed in all the available studies for this short-term time frame. The target MOE for this scenario is 100 (10× for intraspecies extrapolation and 10× for intraspecies variation). No additional safety factor is required because the proposed dose is a NOAEL for an effect (myotonic twitches) that occurred within the first 30 days of the study.

Intermediate-term occupational inhalation exposure (1–6 months)
The endpoint for intermediate-term inhalation exposure is a LOAEL of 1.4 mg/kg bw/day based on treatment-related microscopic lens lesions (cataracts) observed in eyes of female dogs at 13 weeks. The NOAEL could not be determined because 1.4 mg/kg bw was the lowest dose tested in the female dogs in this study. There

is no inhalation study of any duration (other than acute studies) available for famoxadone. The study and endpoint selected for this short-term inhalation risk assessment are based on an oral study with a proposed dose of 1.4 mg/kg bw/day and provide protection from the effects observed in all the available studies for this intermediate-term time frame. Therefore, the oral dose of 1.4 mg/kg bw/day is equivalent to an inhalation dose of 1.4 mg/kg bw/day. The target MOE is 300 (10× for intraspecies extrapolation, 10× for intraspecies variation and 3× because a LOAEL was used).

3.5 Drinking water limit

This section is addressed in Section 4.1.

3.6 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

Tanos 50DF is formulated as dry flowable granules containing 25% famoxadone and 25% cymoxanil. The fungicide will be applied throughout the growing season when the disease is prevalent at the proposed rate of 560–840 g/ha (140–210 g famoxadone/ha). A maximum of 6 applications and a 7-day re-application interval are recommended (see section 7.6). Tanos 50DF must be used in rotation with another fungicide with a different mode of action. A reentry interval (REI) of 12 hours is proposed on the draft label. As well, pre-harvest intervals (PHI) of 3 and 14 days are specified on the draft label for tomatoes and potatoes, respectively.

The proposed personal protective equipment is, "Wear protective clothing such as coveralls over long-sleeved shirt and long pants, goggles or face shield, and chemical-resistant gloves during mixing, loading, application and repair."

Dermal Absorption

In vivo chemical-specific dermal absorption studies conducted with famoxadone were not submitted.

A dermal absorption default of 25% was selected based on a weight-of-evidence approach, including the physical and chemical properties of famoxadone (physical state, high K_{ow}, low water solubility) and the apparent dermal absorption of 5% (calculated by the USEPA).

3.6.1 Operators

There is potential for short-term exposure to farmers, and short- to intermediate-term exposure to custom operators who mix, load and apply the fungicide. As such, the following scenarios will be assessed:

- Farmers and custom applicators mixing/loading dry flowable granular formulation
- Farmers and custom applicators applying liquid using groundboom equipment

The following inputs and parameters were used to calculate mixer/loader/applicator exposures and risks.

$$\text{Daily Exposure (mg/kg/day)} = \frac{UE \times DA \times Rate \times \text{Hectares Treated}}{BW}$$

Where:
UE = Unit Exposure value derived from PHED (mg a.i./kg a.i. handled)
DA = Dermal absorption (%)
Rate = Maximum application rate on product label (0.210 kg ai/ha)
Hectares Treated = Typical number of hectares treated per day (ha/day)
BW = Body weight (70 kg)

$$\text{Total MOE} = \frac{\text{Short- and Intermediate-term NOAEL (mg a.i./kg bw/day)}}{\text{Dose (mg a.i./kg bw/day)}}$$

Mixer/Loader/Applicator (M/L/A) Exposure Estimates
Chemical-specific data for assessing human exposures during pesticide-handling activities were not submitted. Exposure for mixing, loading and applying Tanos 50DF was estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. The PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides.

To estimate exposure for each use scenario, appropriate subsets of data were created from the mixer/loader and applicator database files of PHED. All data were normalized for kg of active ingredient (a.i.) handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. The proposed mixing and loading of the product is open, and application is by open cab groundboom (conventional or air assisted). PHED subsets were created from MIXER/LOADER–Dry Flowable (open mixing and loading), and APPLICATOR–Groundboom Application (Open Cab) scenarios. PHED assessments were conducted for workers wearing cotton coveralls and gloves during mixing and loading but no gloves during application. Raw PHED unit exposures are presented in Table 1a.

Table 1a PHED Unit Exposure, Dry-Flowable Granules Mix/Load, Groundboom Application

Scenario	Unit Exposure (mg a.i./kg a.i. handled)					
	Dermal Body	Dermal Hands	Dermal Total	Dermal Absorbed[a]	Inhalation	Inhalation + Dermal
mixer/loader, open	70.44	21.5	91.94	22.99	1.02	24.01
groundboom applicator, open cab	7.18	14.35	21.53	5.38	0.96	6.34
mixer/loader/applicator	77.62	35.85	113.47	28.37	1.98	30.35

[a] Dermal Absorption: 25%

Typically the same person will mix, load and apply the pesticide. For farmers treating 4 ha of field tomatoes or 65 ha of potatoes per day, and custom operators treating 300 ha of potatoes per day, the quantity of a.i. that could be handled would be 0.84 kg a.i./day for tomatoes (farmer), 13.65 kg a.i./day for potatoes (farmer) and 63 kg a.i./day for potatoes (custom applicator). Daily exposure estimates and MOEs for farmers and custom applicators are presented in Table1b.

Table 1b Exposure Estimates and MOEs for Famoxadone

Crop	Scenario[a]	Exposure Pattern	Daily Exposure[b] µg a.i./kg bw/d	MOE[c]	MOE[d]
Tomato, field	Farmer —open M/L/A	4 ha/day at 0.210 kg a.i./ha	0.36	27460	—
Potato	Farmer —open M/L/A	65 ha/day at 0.210 kg a.i./ha	5.92	1690	—
	Custom Applicator —open M/L/A	300 ha/day at 0.210 kg a.i./ha	27.31	—	38

[a] Cotton coveralls, gloves for M/L, without gloves for A

[b] Dermal Absorption (DA): 25%

[c] Short-term exposure, NOAEL 10 mg/kg bw/d, target MOE 100

[d] Intermediate-term exposure, NOAEL 1.4 mg/kg bw/d, target MOE 300

loading but no gloves during application. Raw PHED unit exposures are presented in Table 1a.

Table 1a PHED Unit Exposure, Dry-Flowable Granules Mix/Load, Groundboom Application

Scenario	Unit Exposure (mg a.i./kg a.i. handled)					
	Dermal Body	Dermal Hands	Dermal Total	Dermal Absorbed[a]	Inhalation	Inhalation + Dermal
mixer/loader, open	70.44	21.5	91.94	22.99	1.02	24.01
groundboom applicator, open cab	7.18	14.35	21.53	5.38	0.96	6.34
mixer/loader/ applicator	77.62	35.85	113.47	28.37	1.98	30.35

[a] Dermal Absorption: 25%

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Potato	Farmer —open M/L/A	65 ha/day at 0.210 kg a.i./ha	5.92	1690	—
	Custom Applicator —open M/L/A	300 ha/day at 0.210 kg a.i./ha	27.31	—	38

[a] Cotton coveralls, gloves for M/L, without gloves for A

[b] Dermal Absorption (DA): 25%

[c] Short-term exposure, NOAEL 10 mg/kg bw/d, target MOE 100

[d] Intermediate-term exposure, NOAEL 1.4 mg/kg bw/d, target MOE 300

Target MOEs are achieved for farmers wearing cotton coveralls over one layer of clothing while mixing, loading and applying Tanos 50DF to tomatoes or potatoes. For custom applicators, the target MOE is not achieved with open mix/load systems and open cab application equipment. However, preliminary data indicate that target MOE will be achieved with data from a chemical-specific in vivo dermal absorption study and an acreage restriction for custom applicators.

3.6.2 Bystanders

NA

3.6.3 Workers

Dislodgeable Foliar Residue (DFR)
A DFR study was submitted for Tanos 50DF. The DFR study was designed to collect data to calculate DFR dissipation curves for DPX-KP481 (25% famoxadone and 25% cymoxanil) on tomatoes at two test sites in California and Florida. The study was conducted using groundboom equipment to treat tomatoes at 420 g a.i./ha, with 2 applications at 5-day intervals. For this assessment, only famoxadone data will be considered.

The DFR study has several limitations including: the application rate in the study is twice the proposed rate, the application frequency is less than the maximum number supported by the efficacy review and the geographical and climatic conditions of the California and Florida sites were not fully representative of Canadian growing regions. Despite these limitations, data obtained from the California site can be used in exposure and risk assessments for the Canadian use pattern. The results from the DFR study are also acceptable as surrogate data for potatoes.

Data from the DFR study were adjusted to reflect the Canadian use pattern. The adjustments resulted in DFR levels of 0.340 $\mu g/cm^2$ for famoxadone following the last application.

Post-application Exposure Estimates
Estimates of potential exposure for workers re-entering treated areas were determined according to the following equation:

$$\textit{Daily Exposure } (\mu g\ a.i./kg\ bw/d) = \frac{DFR \times TC \times D \times DA}{BW}$$

Where:
DFR = dislodgeable foliar residue ($\mu g/cm^2$)
TC = transfer coefficient (cm^2/hr)
D = duration of activity (hr)
DA = dermal absorption (%)
BW = body weight (kg)

Tomatoes are a labour-intensive crop with a number of reentry activities associated with their cultivation. There is potential for short-term exposure to workers during hoeing, moving irrigation equipment, crop scouting, and intermediate-term exposure to workers during sorting fruits on the harvester for processing tomatoes. In fresh market tomatoes, there is potential for intermediate-term exposure to workers during tying, pruning and harvesting fresh market tomatoes. For potatoes, little foliar contact is expected from harvesting but there is potential short- to intermediate-term exposure from scouting, roguing and moving irrigation equipment.

Dupont is a member of the Agricultural Reentry Task Force (ARTF) and therefore has access to ARTF-generated transfer co-efficients. For reentry workers, the predicted DFR levels following the 6th application were coupled with transfer coefficients for specific reentry activities such as tying, pruning and hand harvesting for tomatoes (1000) and during scouting and irrigation for potatoes (1500). Duration of activity for reentry workers were assumed to be an 8-hour workday for tomatoes and 4 hours for potatoes. Exposure estimates and corresponding MOEs for post-application exposure are presented in Table 2.

Table 2 Post-application Exposure Estimates and Corresponding MOE

Active Ingredient	Scenario	Rate	DALA[a]	DFR[b] (μg/cm^2)	Daily Exposure[c] (μg-ai/kg-bw/d)	MOE[d]
Famoxadone	Tomatoes, field—Tying/Pruning /Hand Harvesting	210	0	0.34	19.41	144
		210	3	0.231	6.59	213
		210	6	0.157	4.47	313
	Potatoes—Irrigation, Scouting	210	0	0.34	7.28	192
		210	4	0.203	4.34	322

[a] Day(s) after the last application

[b] Predicted DFR level after the 6th application

[c] Dermal Absorption: 25% (famoxadone)

[d] Famoxadone: LOAEL = 1.4 mg a.i./kg bw/day, MOE = 300

Target MOEs are achieved after 6 days for field tomatoes and 4 days for potatoes. These REIs may be agronomically challenging as tomatoes are a labour intensive crop with a number of reentry activities associated with their cultivation. Preliminary data indicate that exposure estimates will be refined with data from a chemical-specific in vivo dermal absorption study and REI of 24 hours is, therefore, acceptable. A 24-hour interval is consistent with the REI requirement for cymoxanil, the second active ingredient in Tanos 50DF.

Tomatoes are a labour-intensive crop with a number of reentry activities associated with their cultivation. There is potential for short-term exposure to workers during hoeing, moving irrigation equipment, crop scouting, and intermediate-term exposure to workers during sorting fruits on the harvester for processing tomatoes. In fresh market tomatoes, there is potential for intermediate-term exposure to workers during tying, pruning and harvesting fresh market tomatoes. For potatoes, little foliar contact is expected from harvesting but there is potential short- to intermediate-term exposure from scouting, roguing and moving irrigation equipment.

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		210	6	0.157	4.47	313
	Potatoes—Irrigation, Scouting	210	0	0.34	7.28	192
		210	4	0.203	4.34	322

[a] Day(s) after the last application
[b] Predicted DFR level after the 6th application
[c] Dermal Absorption: 25% (famoxadone)
[d] Famoxadone: LOAEL = 1.4 mg a.i./kg bw/day, MOE = 300

Target MOEs are achieved after 6 days for field tomatoes and 4 days for potatoes. These REIs may be agronomically challenging as tomatoes are a labour intensive crop with a number of reentry activities associated with their cultivation. Preliminary data indicate that exposure estimates will be refined with data from a chemical-specific in vivo dermal absorption study and REI of 24 hours is, therefore, acceptable. A 24-hour interval is consistent with the REI requirement for cymoxanil, the second active ingredient in Tanos 50DF.

4.0 Residues

4.1 Food Exposure Assessment

Nature of the Residue in Plants

Famoxadone, radiolabeled either in ^{14}C-phenoxyphenyl or ^{14}C-phenylamino was applied to grapes (600 g a.i./ha/season), potatoes (900 g a.i./ha/season) and field tomatoes (1260 g a.i./ha/season). Negligible levels of ^{14}C-residues (approx. 0.006 ppm) were observed in the potato tuber. Famoxadone was the major component of the extractable ^{14}C-residues in potato foliage with extractable residues in the range of 65.9–97.3% of the total radioactive residues (TRRs) (4.7–23.1 ppm) for Day 0, Day 37 and Day 51 (final harvest). Both IN-JL856 and IN-H3310 were observed as minor degradation products in the foliage surface washes. In general, famoxadone was the major radiolabelled (75–91.4% of the TRRs) component found as tissue-extractable residues in the tomato fruit samples throughout the study. No major radiolabelled metabolite was observed. The majority of the applied ^{14}C-famoxadone on the grape leaves and berries was deposited as surface residues and recovered as the parent compound, famoxadone (79.1–99.6% of the TRRs). IN-H3310 was the only metabolite recovered (<1.4%) in or on the treated grape leaves of the ^{14}C-POP label. Hydrolytic degradation was the primary metabolic pathway for famoxadone in and on plants following direct foliar application.

Confined Accumulation in Rotational Crops

^{14}C-Famoxadone was applied to soil at 400 g a.i./ha/season with plant back intervals (PBIs) of 30 and 120 days, or at 1.2 kg a.i./ha/season with PBIs of 120 and 365 days. Sugar beet, lettuce and wheat were planted as succeeding crops. The extractable ^{14}C-residues in soil decreased over the duration of the study, after both a single or multiple application regime, while the bound residues increased. Approximately 90–93% of the residues dissipated over the course of 120 days following one application per season at 400 g a.i./ha. More than 96–98% of the residues declined 365 days after the final treatment at 1.2 kg a.i./ha. Famoxadone was the only component identified in the soil. For both radiolabels following a single application, famoxadone was the predominant residue in sugar beet, lettuce and wheat forage (30-day PBI only); wheat chaff and wheat straw (30-day and 120-day PBIs). Multiple applications of famoxadone resulted in an increase in the uptake of residues (famoxadone, IN-KZ007, IN-KZ534 and IN-MQ613) in wheat chaff and wheat straw at PBIs of up to 1 year. Famoxadone was the predominant residue in the wheat straw for the POP-label at 365-day PBI. Available data were insufficient to identify and characterize residues on lettuce and sugar beet commodities at PBIs beyond 30 days for both application rates at the expected maximum label use rate.

Field Accumulation in Rotational Crops

Following treatment of a primary crop (tomatoes) with Tanos 50WG, containing 25% famoxadone, at 1260 g a.i./ha, residues of famoxadone in secondary crops of radish (top and root), spinach leaves and wheat (grain, hay, forage, straw) were below the LOQ of the analytical method (0.01 ppm) at normal harvest and at all plant back intervals (17, 33 and 63 days after treatment [DAT]). Residues of 0.050 and 0.055 ppm were found in a single sample of radish tops (leaves) after a rotational interval of 63 days, but this result appeared to be an outlier based on the analytical data obtained for radish tops at rotational intervals of 17 and 33 days. Residue values in soil for each crop matrix at each plant back interval showed a gradual decline. Taking into account the lack of information regarding the nature of the residue in rotational crops, there is insufficient data to concur with a proposed 30-day plant back restriction for all rotational crops. However, a rotation to cereal grains following a minimum plant back of 30 days can be supported, with one year for all other rotated crops.

Nature of the Residue in Animals

Famoxadone, radiolabeled either in ^{14}C-phenoxyphenyl or ^{14}C-phenylamino was administered orally to laying hens and lactating goats at 10 mg/kg food intake/day for 7 consecutive days. The radioactivity was rapidly and extensively eliminated in excreta (82–90% of the TRRs), with less than 0.5% of the administered dose remaining in eggs, milk and tissues. The parent, famoxadone, was the predominant residue identified in muscle, fat, kidney, liver and milk. The main metabolites identified in feces and liver tissues of goat were IN-KZ007, IN-KZ534, IN-KZ532 and IN-KZ000. In hen, only the liver and egg yolk samples were further identified and characterized. IN-KZ007 was the predominant residue identified in egg yolk and liver, while famoxadone, IN-KZ532 and IN-KZ534 were minor components. However, in liver, radioactive residues were not adequately characterized or identified, as 23.5% (0.016 ppm) remained bound. Therefore, the residue of concern for enforcement purposes cannot be defined until the nature of the residue in poultry is adequately understood.

Methods for Residue Analysis of Plants and Plant Products

Several similar methods for grapes, potatoes, cereals, tomato paste and purée were developed for data-gathering and enforcement purposes. The LOQ was reported as 0.02 ppm for grapes, tomatoes, potatoes and barley/wheat grain and 0.05 ppm for barley/wheat straw and green forage. Recoveries in all matrices evaluated were within 73–112% (SD ± 16). The ILVs supported the reliability and reproducibility of the enforcement method for the determinations of famoxadone in grapes, wheat grain, wheat straw and tomato paste.The extraction efficiency of residues of ^{14}C-labelled famoxadone was 111% in tomatoes.

Methods for Residue Analysis of Food of Animal Origin

Two analytical methods for the analysis of famoxadone were developed for data collection and enforcement methods for livestock commodities. Method AMR-3750-96, used as part of the livestock feeding study, consisted of a GLC with NPD to quantitate residues of famoxadone in milk, eggs and animal tissues. The LOQ reported was

0.02 ppm for all bovine and poultry tissues, eggs and milk, except for cream (0.1 ppm). Recoveries of famoxadone were 76–120% (SD ± 12%) in beef muscle, beef fat, whole milk, cream, poultry muscle and eggs. For method DuPont-1452, milk and tissue samples were extracted by MSPD, using octadecylsilyl-derivatized packing as a support and acetonitrile as an eluent. The LOQs were reported as 0.01 ppm (milk, cream, muscle, kidney, fat) and 0.05 ppm (liver). Recoveries ranged from 71% to 113% (SD ± 11%). Method DuPont-1452 has been radiovalidated but has not undergone an ILV. However, this method was determined to be similar enough to the plant matrices method DuPont-1651 that a separate ILV is not required. It should be noted that these methods do not address all of the proposed residues of concern in poultry matrices.

Storage Stability Data—Plant Matrices
Famoxadone residues were stable under frozen storage (−20°C) in potatoes, grapes, wheat forage, straw, grain and soil for up to 18 months.

Crop Field Trials
Twenty-two supervised crop field trials with famoxadone treatment on potatoes were conducted in zones representative of the U.S. and Canada (16 sites at 1260 and 6 at 1680 g a.i./ha).

The maximum residues in potatoes, collected 14 days after the last application, were equal to or less than 0.02 ppm (LOQ). Eighteen crop field trials were conducted on field tomatoes throughout the U. S. (Pennsylvania, Maryland, Florida, New York, Georgia, Illinois, Arizona, California, Indiana). Maximum residues in tomatoes, collected 3 days following the last application of famoxadone treatment at 1260 g a.i./ha/season, were 0.79 ppm with a supervised trial median residue (STMR) value of 0.25 ppm. Residue decline studies showed that with increasing pre-harvest intervals (PHIs), residues of famoxadone had a tendency to dissipate slowly within 20 days (Zone 2) and more rapidly within 5 days (Zone 3).

Processed Food/Feed
DPX-KP481 50WG was applied to potatoes at 6.3 kg a.i./ha/season (PHI 14 days) and to tomatoes at 7.7 kg a.i./ha/season (PHI 3 days). The potato samples were processed into potato wet peel, potato chips and potato granules. The tomatoes were processed into paste and purée. A comparison of the residues in the raw potato and tomato with those in their processed fractions resulted in a concentration factor of 1.7, 1.3 and 0.4 for wet potato peel, tomato paste and tomato purée, respectively.

Meat/Milk/Poultry/Eggs
Lactating cattle (*Bos Taurus*) were administered orally 9, 27 and 90 μg famoxadone/g feed for 28 consecutive days. Residue concentrations in muscle, fat, liver and kidney were linearly related to the dose. In whole milk, residue levels of famoxadone reached a plateau by the tenth day of dosing for all three treatment levels. Based on a diet of potato culls and process waste, the maximum theoretical dietary burden was calculated as 0.1 ppm. The anticipated meat, meat by-products and milk residues resulting from the

feeding of famoxadone in treated crops are at or below the respective LOQs of the tissues. Based on the fact that residues of famoxadone transferred into the cream portion of milk, a maximum residue limit (MRL) is warranted at 0.06 ppm for milk fat. At this time, there is no proposed use for famoxadone that would result in residues on significant poultry feed items and a poultry feeding study is not required.

Dietary Risk Assessment
The proposed domestic use of famoxadone (Tanos 50DF) on potatoes and tomatoes does not pose an unacceptable chronic dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and Behaviour in the Environment

5.1 Physical and chemical properties relevant to the environment

Physical and chemical properties relevant to the environment are presented for famoxadone in Appendix III, Table 1. Famoxadone is practically insoluble to sparingly soluble in water over the range of pH 5 to pH 9. The vapour pressure of famoxadone and Henry's Law Constant indicate that famoxadone is not likely to volatilize from water or moist soil surfaces. The log K_{ow} values indicate a potential for famoxadone to bioaccumulate. The dissociation constant could not be measured directly due to the low solubility in water. Based on the chemical structure, famoxadone is expected to be weakly basic. The maximum light adsorption was at 231 nm, indicating that famoxadone is not likely to undergo phototransformation.

5.2 Abiotic transformation

A summary of abiotic transformation processes is presented for famoxadone in Appendix III, Table 2. Hydrolysis indicated that the first-order half-lives of famoxadone at pH 5, pH 7 and pH 9 were 31–41 days, 2–2.7 days and 1.5–1.8 hours, respectively. Major transformation products included IN-JS940, IN-JL856, IN-H3310 and IN-MN968. The study was terminated before the formation and decline of significant transformation products had been fully addressed. Hydrolysis of the parent compound is pH-dependent and the rate of transformation increases with increasing pH. Under neutral to basic conditions hydrolysis is an important route of transformation for famoxadone.

Phototransformation of famoxadone in aqueous solution occurred with first-order half-lives of 41 days and 1.1–1.9 days in the dark and irradiated samples, respectively. The major transformation products detected were IN-JS940 and IN-H3310. Concentrations for all transformation compounds were still increasing at test termination. The study was terminated before the formation and decline of significant transformation products had been fully addressed.

Phototransformation indicated that the first-order half-lives of famoxadone on soil ranged from 3.4 days to 5.8 days in the irradiated soils. The half-life of famoxadone in the dark control soil was determined to be ≥30.8 days. The transformation products IN-MN468 and IN-MN467 only occurred in the soil phototransformation study.

Phototransformation in water and on soil may be important routes of transformation.

5.3 Biotransformation

A summary of biotransformation is presented for famoxadone in Appendix III, Table 3. Famoxadone was non-persistent under aerobic soil conditions with DT_{50} values ranging from 2 days to 11 days. In all soils, the aerobic biotransformation was biphasic with a relatively rapid rate occurring during the initial period and a subsequent decline in the transformation rate. Two major transformation products were detected, IN-KZ007 and IN-JS940, however, each of these was only detected in one of the five soils tested. The minor transformation products detected in all soils were IN-KZ007, IN-JS940 and IN-MN467. The DT_{50} values for the transformation products IN-KZ007, IN-KF015 and IN-JS940 in soil were 1.5–10.3 days, 1.2 days and 6–23 hours, respectively. Under anaerobic soil conditions, famoxadone was slightly persistent with a DT_{50} of 28 days. The major transformation product formed under anaerobic soil conditions was IN-JS940, with minor transformation products IN-KZ007 and IN-H3310 also being formed. Famoxadone was non-persistent in aerobic water/sediment studies with DT_{50} values in the whole system ranging from 0.68–2.05 days. The major transformation products identified in the water and sediment separately were IN-JS940 and H3310, respectively. The minor transformation products identified in both water and sediment were IN-KZ007, IN-JS940, IN-H3310 and IN-JL856. The aerobic water/sediment study showed that there was partitioning of famoxadone from the water to the sediment. All the studies indicated that famoxadone is fully transformed to bound residues and carbon dioxide.

5.4 Mobility

The adsorption/desorption studies indicated that famoxadone is slightly mobile in all the soils studied, IN-KZ007 has low mobility or is immobile, IN-KF015 has low to high mobility and IN-JS940 has low to very high mobility. Based on vapour pressure and Henry's Law Constant, data on the volatility of famoxodone are not required.

5.5 Dissipation and accumulation under field conditions

Laboratory studies of biotransformation indicated that famoxadone is non-persistent in aerobic soil with the formation of major transformation products IN-KZ007 and IN-JS940 in one of the five soils tested. Since major transformation products were only recorded in one of five soils, the applicant stated that transformation products would not be significant in the environment and, therefore, they did not measure for transformation products in the field dissipation studies. The Canadian and U.S. field dissipation studies demonstrated the dissipation of the parent compound, however, there was no analysis for transformation products. Sites that were representative of Canadian growing areas included the Ecoregions 5.3, 8.1, 9.2 and 10.1. DT_{50} and DT_{90} values for famoxadone at the sites in these Ecoregions ranged from 5–26 days and 17–92 days, respectively. Based on these DT_{50} values, famoxadone would be classified as non-persistent to slightly persistent in soil under field conditions. This was supported by the carryover values, which were <4.4% of the applied parent compound after one year's sampling. At all sites, famoxadone was detected primarily in the top 0–15 cm soil depth. This indicated that the famoxadone was relatively immobile and leaching was not likely to be an important route of dissipation under field conditions. There was good agreement between laboratory and field studies on persistence and mobility of famoxadone in soil.

5.6 Bioaccumulation

The log K_{ow} of famoxadone at pH 7 is 4.65, indicating a potential for bioaccumulation. Bioaccumulation of famoxadone (phenoxyphenyl- and phenylamino-labelled) was studied in juvenile bluegill sunfish under flow-through conditions with famoxadone at a nominal concentration of 0.24 mg/L and 2.4 μg/L. The exposure periods were 9–28 days. Following the exposure periods, fish were transferred to clean aquaria for a 14-day depuration period.

During the exposure period, the concentration of total radioactivity in fish tissue reached steady state within 7–9 days. Mean total residues at steady state were highest in the nonedible tissue compared to the edible and whole fish tissues for both labels. Analysis of the 9-DAT phenylamino-labelled samples indicated that famoxadone was the primary radioactive component recovered from the fish tissues at the end of the accumulation phase.

Bioconcentration factors for both label treatments were 971–1286× for the edible, 3327–3608× for the nonedible and 2434–3425× for the whole fish tissues. Depuration was rapid in the 0.240 μg/L phenoxyphenyl-label and 2.4 μg/L phenylamino-label treatment systems, with 50% of the total [^{14}C]residues accumulated by 28 and 14 DAT, respectively, eliminated by day 2 of the depuration period and >90% of the accumulated residues by day 7 of the depuration phase. Because of the rapid depuration of famoxadone, bioaccumulation is not expected to be a concern.

5.7 Summary of fate and behaviour in the terrestrial environment

A summary of fate and behaviour of famoxadone in the terrestrial environment is presented in Appendix III, Table 4. Laboratory studies of transformation in soil indicated that hydrolysis and biotransformation are important famoxadone transformation routes and that phototransformation on soil is a potential route. Hydrolysis is rapid in neutral and alkaline solutions but slow in acidic solutions. The major transformation products were IN-JS940, IN-H3310, IN-JL856 and IN-MN968. The phototransformation study of famoxadone on soil indicated that the half-lives on soil were 30.8 d and 3.4–5.8 d for the dark and irradiated samples, respectively. Based on the biotransformation DT_{50} values, famoxadone was non-persistent in aerobic soil and slightly persistent in anaerobic soils.

The major transformation product IN-JS940 formed in both aerobic and anaerobic soils, while IN-KZ007 formed only in aerobic soils. Biotransformation DT_{50} values for the transformation products IN-KZ007, IN-KF015 and IN-JS940 indicated the non-persistence of these compounds. The applicant did not consider the transformation products IN-H3310 and IN-MN468 to be persistent in the environment, therefore, aerobic soil biotransformation and adsorption/desorption studies were not performed using these compounds. Sites that were representative of Canadian growing areas were situated in Ecoregions 5.3, 8.1, 9.2 and 10.1. DT_{50} and DT_{90} values, from field studies with famoxadone performed on sites within the Ecoregions listed above, ranged from 5–26 days and 17–92 days, respectively. Based on the DT_{50} values, famoxadone would be classified as non-persistent to slightly persistent under Canadian field conditions. This was supported by the carryover values, which were <4.4% of the applied parent compound after one year sampling. At all sites, famoxadone was detected primarily in the top 0–15 cm soil depth. This indicated that the famoxadone was relatively immobile and leaching was not likely to be an important route of dissipation under field conditions. There was good agreement between laboratory and field studies on persistence and mobility of famoxadone in soil.

5.8 Summary of fate and behaviour in the aquatic environment

A summary of fate and behaviour of famoxadone in the aquatic environment is presented in Appendix III, Table 5. Hydrolysis of famoxadone is an important route of transformation in the aquatic environment at neutral ($t_{1/2}$ = 2–2.7 d) and alkaline ($t_{1/2}$ = 1.6–1.8 d) pHs. Phototransformation may be an important route of transformation in surface waters. The aqueous phototransformation half-life ranges from 1.1 to 1.9 days (under continous irradiation) with the formation of IN-JS940 and IN-H3310 as the major transformation products. The study was terminated before the formation and decline of transformation products had been fully addressed, as concentrations for all transformation products were still increasing at test termination (irradiated and dark samples). The biotransformation study in aerobic water/sediment indicated that famoxadone is non-persistent with DT_{50} values in the whole system ranging from 0.68 to 2.05 days. IN-JS940 was the major transformation product formed in water and IN-H3310 was the major transformation product formed in sediment. The aerobic water/sediment study showed that there was partitioning of famoxadone from the water to the sediment. Famoxadone predominantly mineralized to CO_2, or was incorporated as unextractable residues.

5.9 Expected environmental concentrations

The maximum annual application rate of Tanos 50DF on potatoes and field tomatoes for Canada is 5.04 kg/ha (containing 1.26 kg famoxadone/ha and 1.26 kg cymoxanil/ha). To obtain the maximum annual application rate, Tanos 50DF may be applied at a rate of 560–840 g/ha (140–210 g famoxadone/ha plus 140–210 g cymoxanil/ha) for a maximum of 6 applications. Tanos 50DF is to be applied at minimum 7-day intervals.

5.9.1 Soil

The expected environmental concentration (EEC) of famoxadone on soil was calculated based on a soil density of 1.5 g/cm^3 and soil depth of 15 cm and using the maximum Canadian label application rates. The field dissipation DT_{50} of 26 days (Ecoregion 8.1) was used to account for the dissipation of famoxadone between applications. When the DT_{50}, the minimum application interval, the number of applications per year, and the low (140 g famoxadone/ha) and high (210 g famoxadone/ha) application rates are considered, the maximum annual cumulative application rates were estimated to be 554 g a.i./ha for the lower treatment rate and 831 g a.i./ha for the higher treatment rate. The EECs in soil corresponding to these cumulative application rates were 0.25 mg a.i./kg soil and 0.37 mg a.i./kg soil, respectively, for potatoes and tomatoes.

5.9.2 Aquatic systems

The EEC of famoxadone in water was calculated using the whole system DT_{50} of 2.05 d (pH 7.7) from the aerobic water/sediment biotransformation study. When the DT_{50}, the application interval, the number of applications per year, and the low (140 g famoxadone/ha) and high (210 g famoxadone/ha) application rates were considered, the maximum annual cumulative application rates from direct over-spray in surface waters at 30 cm water depth were estimated to be 155 g a.i./ha for the lower treatment rate and 232 g a.i./ha for the higher treatment rate. The EECs in water corresponding to these cumulative application rates were 0.051 mg a.i./L and 0.077 mg a.i./L, respectively, for potatoes and tomatoes.

Based on the potential use pattern of famoxadone in areas where potatoes and field tomatoes are grown, residues of famoxadone in potential drinking water sources in these areas were modelled using the LEACHM (for groundwater) and PRZM/EXAMS (for surface water). The model was run using conservative scenarios, the environmental profile of famoxadone, and an application rate of 0.21 kg ai/ha applied six times at intervals of seven days. The Level I estimated environmental concentrations of famoxadone in drinking water were 6.23 μg a.i./L and 0.12 μg a.i./L for acute (90th percentile of yearly peaks) and chronic (90th percentile of yearly averages) exposures, respectively. These numbers were reported to the Food Residue Exposure Assessment Section (FREAS) for human health assessment.

However, since the modelling results from the Level I screening model failed the human health assessment conducted by the PMRA, a refined analysis was conducted (Level II). The Level II analysis represents a less conservative approach to predicting drinking water concentrations of the active ingredient as it more accurately reflects the use pattern of the chemical. Two scenarios typical of the potato-growing regions were used in the water modelling: one for Prince Edward Island and a second for Manitoba. As the Level I modelling indicated that drinking water values in reservoirs were higher, the Level II modelling was performed for only the reservoir scenario. The soil type and values for K_d and K_{oc} were futher refined to more accurately represent the soils on which potatoes would be grown. Ten separate scenarios were run in which famoxadone was applied at an application rate of 0.21 kg a.i./ha for six consecutive applications at intervals of seven days. The start dates of each scenario were either the 1st or 15th of each month that famoxadone is typically used (information from the Efficacy and Sustainability Assessment Division (ESAD)). As was requested, a refined Level II assessment was performed for the active ingredient, famoxadone, as well as for famoxadone in conjunction with the major transformation products of concern.

The most conservative Level II estimates of the EECs in drinking water sources for famoxadone were 4.04 μg a.i./L (acute) and 0.097 μg a.i./L (chronic), while the corresponding values for famoxadone plus transformation products were 9.12 μg a.i./L (acute) and 0.25 μg a.i./L (chronic). These values were provided for the human health assessment. As a Level II drinking water assessment was conducted, any futher use expansion beyond potato- and tomato-growing regions will require a reevaluation of drinking water concentrations for three reasons: the environmental fate of the major transformation products may be better understood at that time, the use of famoxadone may be expanded to new crops for which drinking water scenarios were not modelled at Level II and concentrations in dugouts were not examined.

5.9.3 Vegetation and other food sources

Since data were not available on the residues of famoxadone in wildlife food sources immediately following application, the expected environmental concentrations of famoxadone were estimated (Appendix III, Table 6) using a standard scenario based on the correlations of Hoerger and Kenaga (1972) and Kenaga (1973) as modified by Fletcher (1994) using the maximum annual Canadian label rate for Tanos 50DF of 1.26 kg/ha. No information was available on the dissipation of famoxadone on wildlife food sources; therefore, it was assumed that no dissipation occurred.

The concentrations of famoxadone in the diets of standard birds and mammals are estimated by considering the proportion of each food type that the particular species would consume in their diet. Taking into consideration the EEC determined for that food type and the proportion of the diet consisting of that particular food source, it is possible to estimate the amount of famoxadone that could be consumed in the diet (Appendix III, Table 7).

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The effects of famoxadone on terrestrial organisms are presented in Appendix III, Table 8. The acute (14-d) LC_{50} and no observable effect concentration (NOEC) of famoxadone to the earthworm (*Eisenia foetida*) were 470 mg a.i./kg soil and 62.5 mg a.i./kg soil, respectively. The acute (48-h) contact LC_{50} and NOEC of famoxadone to the honey bee (*Apis mellifera*) were >25 μg a.i./bee and 25 μg a.i./bee, respectively. The corresponding acute oral (48-h) LC_{50} and NOEC were >400 μg a.i./bee and 400 μg a.i./bee, respectively. Famoxadone, therefore, is classified as practically non-toxic to the honey bee according to the criteria of Atkins et al. (1981).

Several studies were conducted to determine the effect of famoxadone on beneficial insects. According to classification by Hassan et al. (1994), an application of 0.7 kg DPX-KP481/ha (25% famoxadone and 25% cymoxanil) is not potentially harmful to green lacewings. No harmful effects were observed in ground beetles or staphylinid beetles when treated with an application of 0.7 kg DPX-KP481/ha. Using the same application rate of DPX-KP481, there was a 28–69% reduction in reproductive success, relative to the controls, in hoverflies. Therefore, a treatment of 0.7 kg DPX-KP481/ha is considered potentially harmful to hoverflies. The end-use products DPX-KX007 SC and DPX-KX007 WG were found to be slightly harmful to harmful to predatory mite studies.

The acute (14-d) oral LD_{50} and no observable effect level (NOEL) of famoxadone to the bobwhite quail (*Colinus virginianus*) were >2250 mg a.i./kg bw and 2250 mg a.i./kg bw, respectively. The acute (14-d) oral LD_{50} and NOEL of the end-use product DPX-KX007-5 WG (22.7% famoxadone and 30.4% cymoxanil) to the bobwhite quail were >2250 mg DPX-KX007-5 WG/kg bw and 292 mg DPX-KX007-5 WG/kg bw, respectively. For both the bobwhite quail and the mallard duck, the subacute (8-d) dietary LC_{50} and NOEL of famoxadone were >5620 mg a.i./kg diet and 5620 mg a.i./kg diet, respectively. For both the bobwhite quail and the mallard duck, the NOEC and LOEC of famoxadone on the reproduction were 46 mg a.i./kg diet and 252 mg a.i./kg diet, respectively. Based on the results of the toxicity studies, famoxadone is classified as practically non-toxic to bobwhite quail on an acute and dietary basis and to mallard ducks on a dietary basis. Reproduction in bobwhite quail and mallard ducks exposed to famoxadone, however, was significantly reduced as compared to the controls.

Famoxadone has a low toxicity to rats on an oral and inhalation basis and low toxicity to rabbits on a dermal basis. Tanos 50DF is moderately toxic to rats on an oral basis and has low toxicity to rats on a dermal and inhalation basis. Famoxadone was found to be slightly irritating to the eye and minimally irritating to the skin of rabbits and non-sensitizing to the skin of guinea pig. Tanos 50DF was mildly irritating to the eye and minimally irritating to the skin of rabbits and non-sensitizing to the skin of guinea pigs.

In 90-day dietary tests, the NOAELs of famoxadone for rats, mice and dogs were 3.34 and 4.24 mg/kg bw/d, 62.4 and 79.9 mg/kg bw/d and NA and 1.3 mg/kg bw/d in males and females, respectively. The most common indicators of toxicity were hepatotoxicity and hematological changes consistent with anemia. Famoxadone also induced treatment-related cataracts and microscopic lens lesions in dogs.

Oncogenicity studies with mice and rats indicated effects in the liver, centrilobular effects, slight hepatotoxicity and hemolytic anemia (NOAEL 96/130 and 8.4/2.2 mg/kg bw/d for M/F, respectively). There was, however, no evidence of oncogenicity. Effects were observed but oncongenicity was not established in dogs or monkeys, however, a NOAEL was established for the monkey at 100 mg/kg bw/d. Famoxadone was not genotoxic and non-mutagenic in most studies, with the exception of studies performed with human lymphocytes in which genotoxicity was positive. However, the biological relevance of these results was unclear since the effect was limited to the nonactived phase of testing. No immunotoxic effects were observed in rats or mice. Neurotoxic effects were observed in some of the studies with rats and dogs.

In a 2-generation reproduction study with rats, famoxadone was not a reproductive toxicant and there was no qualitative evidence of increased susceptibility in offspring (NOAEL 11.3/14.2 mg/kg bw/d for M/F, maternal and offspring effects). In develpomental toxicity studies with rats and rabbits, famoxadone effects included decreased weight and food consumption in rats (NOAEL 250 mg/kg bw/d, maternal) and rabbits (NOAEL 350 mg/kg bw/d, maternal and developmental), as well as increased abortion numbers in the rabbits. Famoxadone was non-teratogenic to rats and rabbits, and there was no evidence of increased susceptibility to the young.

Studies on the effect of the end-use product DPX-JE874 10EC (famoxadone 9.2%) on seedling emergence and vegetative vigour of monocot plant species (*Allium cepa*, onion; *Zea mays*, corn; *Triticum aestivum*, winter wheat; *Sorghum bicolor*, sorghum) and dicot plant species (*Beta vulgaris*, sugar beets; *Glycine max*, soybean; *Pisum sativum*, pea; *Lycopersicon esculentum*, tomato; *Brassica napus*, rape; *Cucumis sativus*, cucumber) indicated that there was no significant inhibition of seedling emergence or vegetative vigour. The EC_{25} and NOEC were >2.28 kg DPX-JE874 10EC/ha and 2.28 kg DPX-JE874 10EC/ha, respectively.

6.2 Effects on aquatic organisms

The effects of famoxadone on aquatic organisms are presented in Appendix III, Table 9.

Freshwater

The acute (48-h) EC_{50} of famoxadone to the water flea (*Daphnia magna*) was 11.8 μg a.i./L. The acute (48-h) EC_{50} of the transformation product IN-JS940 to the same species was >9600 μg/L. The chronic (21-d) NOEC of famoxadone to the water flea was 0.085 μg a.i./L. The corresponding EC_{50} (28-d) for the sediment-dwelling stage of the midge (*Chironomus riparius*), when applied directly to water, was 410 μg a.i./L.

The acute LC_{50}s of famoxadone to the rainbow trout (*Oncorhynchus mykiss*) and the bluegill sunfish (*Lepomis macrochirus*) were 12 μg a.i./L (48-h) and 13 μg a.i./L (96-h), respectively. The chronic (90-d) NOEC of famoxadone to the rainbow trout was 1.4 μg a.i./L. The acute LC_{50} (96-h) of the transformation product IN-JS940 to the rainbow trout was >9600 μg/L.

The acute EC_{50} (120-h) of famoxadone to the algae *Selenastrum capricornutum* and *Anabaenea flos-aquae* were 23 μg a.i./L and >84.3 μg a.i./L, respectively. The 120-h algae EC_{50} study for the diatom *(Navicula pelliculosa)* was determined to be deficient and did not fulfill the USEPA's guideline requirements. The acute (14-d) NOEC of famoxadone to the duckweed (*Lemna gibba*) was 81 μg a.i./L.

Based on the results of the freshwater toxicity studies, famoxadone is very highly toxic to *Daphnia magna*, rainbow trout and bluegill sunfish. Famoxadone applied directly to water was found to be highly toxic to midges. The acute studies using IN-JS940 indicated that this transformation product is, at most, slightly toxic to rainbow trout and Daphnia magna. The most sensitive freshwater aquatic toxicity endpoint was the 21-d NOEC (0.085 μg a.i./L) for *Daphnia magna*.

Marine

The acute (96-h) LC_{50} of famoxadone to the saltwater mysid (*Mysidopsis bahia*) and the acute (96-h) EC_{50} (for shell deposition) to the eastern oyster (*Crassostrea virginica*) were 3.9 μg a.i./L and 1.41 μg a.i./L, respectively. The chronic (28-d) EC_{50} and NOEC for the mysid were 2.98 μg a.i./L and 0.83 μg a.i./L, respectively.

The acute (96-h) LC_{50} and the chronic (36-d) NOEC of famoxadone to the sheepshead minnow (*Cyprinodon variegatus*) were 49.4 μg a.i./L and 5.58 μg a.i./L, respectively.

The acute (48-h) EC_{50} of famoxadone to a marine diatom (*Skeletonema costatum*) was 41.5 a.i./L.

Based on the results of the marine toxicity studies, famoxadone is very highly toxic to mysid shrimp and sheepshead minnow. The mollusk shell deposition study also indicated that famoxadone is very highly toxic. The most sensitive marine aquatic toxicity endpoint was the 28-d NOEC (0.83 μg a.i./L) for shrimp.

6.3 Effects on biological methods of sewage treatment

Not applicable for the proposed use.

6.4 Risk characterization

Risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The Environmental Assessment Division (EAD) currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the margin of safety (MOS), which is the ratio of the toxicity endpoint to the EEC. The endpoint used for both acute and chronic toxicity is the NOEC from the appropriate laboratory study. Those cases for which a NOEC was not reported, the value was estimated as 0.1 × LD_{50} or 0.1 × LC_{50}. Risks were then classified based on the scheme presented in Table 6.4.

For birds and mammals the number of days of intake of active ingredient by a wild species equivalent to a gavage-administered dose that killed 50% of the individuals in the lab population (number of days to LD_{50}) was also calculated. The number of days to LD_{50} was determined by calculating the LD_{50} of an individual (LD_{50} × BWI) and dividing it by the daily intake of active ingredient (EEC in food × mean food consumption [FC]). The number of days of intake of active ingredient by a wild species equivalent to a dose administered by gavage that would reach the no observed effect level was calculated in the same manner except the NOEL was used instead of the LD_{50}.

6.4.1 Environmental behaviour

Laboratory studies of transformation in soil indicated that hydrolysis and biotransformation are important famoxadone transformation routes, and that phototransformation on soil is a potential route. Hydrolysis is rapid in neutral and alkaline solutions, but slow in acidic solutions. The major transformation products were IN-JS940, IN-H3310, IN-JL856 and IN-MN968. Phototransformation of famoxadone on soil indicated that the half-lives on soil were 30.8 days and 3.4–5.8 days for the dark and irradiated samples, respectively. Based on the biotransformation DT_{50} values, famoxadone was non-persistent in aerobic soils and slightly persistent in anaerobic soils. The major transformation product IN-JS940 formed in both aerobic and anaerobic soils, while IN-KZ007 was formed only in aerobic soils. Biotransformation DT_{50} values for the transformation products IN-KZ007, IN-KF015 and IN-JS940 indicated the non-persistence of these compounds. Since the applicant did not consider the transformation products IN-H3310 and IN-MN468 to be persistent in the environment, aerobic soil biotransformation and adsorption/desorption studies were not performed using these compounds. Sites that were representative of Canadian growing areas were situated in Ecoregions 5.3, 8.1, 9.2 and 10.1. DT_{50} and DT_{90} values, from field studies with famoxadone performed on sites within the Ecoregions listed above, ranged from 5–26 days and 17–92 days, respectively. Based on the DT_{50} values, famoxadone would be classified as non-persistent to slightly persistent under Canadian field conditions. This was supported by the carryover values, which were <4.4% of the applied parent compound after one year's sampling. At all sites, famoxadone was detected primarily in the top 0–15 cm soil depth. This indicated that famoxadone was relatively immobile and leaching was not likely to be an important route of dissipation under field conditions.

There was good agreement between laboratory and field studies on persistence and mobility of famoxadone in soil.

Hydrolysis of famoxadone is an important route of transformation in the aquatic environment at neutral ($t_{½}$ = 2–2.7 d) and alkaline ($t_{½}$ = 1.6–1.8 d) pHs. Phototransformation may be an important route of transformation in surface waters. The aqueous phototransformation half-life ranges from 1.1 to 1.9 days (under continous irradiation) with the formation of IN-JS940 and IN-H3310 as the major transformation products. The study was terminated before the formation and decline of transformation products had been fully addressed as concentrations for all transformation products were still increasing at test termination (irradiated and dark samples). The biotransformation study in aerobic water/sediment indicated that famoxadone is non-persistent with DT_{50} values in the whole system ranging from 0.68–2.05 days. IN-JS940 was the major transformation product formed in water and IN-H3310 was the major transformation product formed in sediment. The aerobic water/sediment study showed that there was partitioning of famoxadone from the water to the sediment. Famoxadone predominantly mineralized to CO_2, or was incorporated as unextractable residues.

6.4.2 Terrestrial organisms

The risk of famoxadone to terrestrial organisms is presented in Appendix III, Table 10.

Earthworms
As the maximum EEC of famoxadone in soil is 0.37 mg a.i./kg soil and the NOEC for earthworms is 62.5 mg a.i./kg soil, famoxadone will not pose a risk to earthworms at the proposed use rates. The MOS (NOEC ÷ EEC) is 169.

Honeybees
The dietary NOEC for famoxadone was 1000 mg a.i./L. Famoxadone is practically non-toxic to honey bees on an acute contact basis. Famoxadone is not expected to pose a risk, based on inherent toxicity, to bees when Tanos 50DF is applied at the label rates.

Other beneficial insects
According to Hassan et al. (1994), the end-use product DPX-KP481 (25% famoxadone and 25% cymoxanil) applied at 0.7 kg/ha is classified as harmless to green lacewings, ground beetles and staphylinid beetles. At this rate, DPX-KP481 treatments resulted in a 28–69% reduction in reproductive success, relative to the controls, in hoverflies and is, therefore, potentially harmful to foliage-dwelling predators. The end-use products DPX-KX007 SC and DPX-KX007 WG were found to be slightly harmful to harmful to predatory mite (supplemental study).

Wild birds
Wild birds, such as bobwhite quail and mallard ducks, could be exposed to famoxadone residues as a result of consumption of treated vegetation, contaminated prey, or spray drift. The bobwhite diet may consist of approximately 30% small insects, 15% forage

crops and 55% grain and seeds. The EEC of famoxadone in the bobwhite diet after the application of Tanos 50DF, based on the maximum application rate (1260 g a.i./ha) is 220.6 mg a.i./kg dw diet. The mallard duck diet consists of approximately 30% large insects and 70% grain and seeds. The EEC in the mallard diet is 42.6 mg a.i./kg dw diet.

In the acute oral toxicity study with famoxadone, the mean body weight (BWI) of bobwhite quail in the control treatment was 0.209 kg bw/individual, while the mean food consumption (FC) was 0.017 kg dw of diet/individual/d. The potential daily intake of famoxadone (DI = FC × EEC) was calculated as 3.75 mg a.i./individual/d. The reported LD_{50} and NOEL values were >2250 and 2250 mg a.i./kg bw, respectively. When expressed on a per individual basis, the $LD_{50(individual)}$ (= LD_{50} × BWI) was >470 mg a.i./individual and the $NOEL_{(individual)}$ (= NOEL × BWI) was 470 mg a.i./individual. Based on the DI, the $LD_{50(individual)}$ and the $NOEC_{(individual)}$, it would take a bobwhite quail at least 125 continuous days of consumption of a contaminated diet to attain the dose equivalent to that administered in the laboratory by gavage that had no observable effect on the laboratory population.

Dietary studies with both the bobwhite quail and the mallard duck indicated that the NOECs (5620 mg a.i./kg dw of diet) were greater than the EEC for these species. The MOS (MOS = NOEC ÷ EEC) were 26 and 132, respectively. The reproductive studies in bobwhite quail and mallard duck indicated a NOEC of 46 mg a.i./kg dw of diet. The MOS, based on reproduction parameters, is 0.21 for bobwhite and 1.1 for mallard ducks. Famoxadone will not pose a dietary risk to birds, however it will pose a moderate reproductive risk when Tano 50DF is applied at the maximum rate.

Wild Mammals

Wild mammals, such as rats and mice, could be exposed to residues of famoxadone as a result of the consumption of sprayed vegetation and/or contaminated prey. From Appendix III, Table 7, assuming no transformation and no interception of orchard blast spray, the EECs of famoxadone in the diets of rats and mice were 635.7 and 631.8 mg a.i./kg dw diet, respectively.

For rats, BWI was 0.35 kg and FC was 0.06 kg/individual/d. Therefore, the daily intake (DI = FC × EEC) of famoxadone was 38 mg/individual/d. The acute oral LD_{50} for famoxadone in the rat is 3100 mg/kg bw. Expressed on a per individual basis, the $LD_{50(individual)}$ (LD_{50} × BWI) is 1085 mg/individual. Based on the DI and the $LD_{50(individual)}$, it would take a rat at least 28 continuous days of feeding to attain the dose equivalent to that administered in the laboratory by gavage that killed 50% of the laboratory population. As a NOEL was not available for the study, one-tenth of the LD_{50} was used as the NOEL. The calculated NOEL is 310 mg/kg bw, therefore, based on the DI and the $NOEL_{(individual)}$, it would take a rat 2.8 continuous days of feeding to attain the dose equivalent to a dose administered by gavage that would reach the no observed effect level. Based on the above assessment, application of famoxadone at the maximum proposed label rate will not pose an appreciable risk on an acute basis to populations of wild mammals that are exposed to famoxadone in their diet.

The NOAELs for the dietary toxicity studies with rats (NOAEL = 50 mg/kg dw diet) and mice (NOAEL = 350 mg/kg dw diet), as well as the NOAEL for the reproductive study with the rat (NOAEL = 200 mg/kg dw diet) were all lower than the respective EECs, therefore, famoxadone poses a moderate to high risk to rats and mice on a chronic basis when applied at the proposed maximum application rate. The corresponding MOSs are 0.08, 0.55 and 0.31.

Vascular plants
No effects on seedling emergence or vegetative vigour were observed in the terrestrial plant studies using the end-use product DPX-JE874 10EC (famoxadone 9.2%), thus, the EC_{50} is >2.28 kg/ha. The proposed single application rates for Tanos 50DF (25% famoxadone and 25% cymoxanil) are 0.56 kg/ha or 0.84 kg/ha. Famoxadone applied at the maximum use rate to the soil surface prior to plant emergence, or directly to the foliage of growing plants, poses a low risk to terrestrial plants.

6.4.3 Aquatic organisms

The risk of famoxadone to aquatic organisms is presented in Appendix III, Table 11.

Non-target freshwater

Invertebrates
The most sensitive endpoint was the NOEC (0.085 μg a.i./L) based on the number of *Daphnia magna* offspring produced. This is also the most sensitive freshwater aquatic endpoint. The EEC in water after the application of Tanos 50DF was 77 μg a.i./L, therefore, there is very high risk to fresh water invertebrates at the proposed maximum rate of Tanos 50DF. The MOS is 0.001.

Fish
The most sensitive endpoint was the chronic NOEC (1.4 μg a.i./L), based on the percentage of abnormalities in surviving fish at test termination. Based on the EEC, there is high risk to fish at the proposed maximum application rate of Tanos 50DF. The MOS is 0.02.

Algae
The most sensitive endpoint was the NOEC (3.9 μg a.i./L), based on biomass, for freshwater algae. The MOS is 0.05, thus, there is high risk to freshwater algae at the proposed maximum application rate of Tanos 50DF.

Aquatic plants: The most sensitive endpoint was the NOEC (81 μg ai/L), based on frond density and biomass, for *Lemna gibba*. The MOS is 1.05, thus, there is low risk to aquatic plants at the proposed maximum application rate of Tanos 50DF.

Non-target marine

Invertebrates

The most sensitive marine invertebrate endpoint is the chronic NOEC (0.83 μg a.i./L), based on survival, for mysid shrimp. This is also the most sensitive marine aquatic endpoint. The MOS is 0.01, thus, there is high risk to marine invertebrates at the proposed maximum application rate of Tanos 50DF.

Fish

The most sensitive marine fish endpoint is the chronic NOEL (5.58 μg a.i./L), based on hatch survival, for sheepshead minnow. Based on the EEC, there is high risk to marine fish at the proposed maximum application rate of Tanos 50DF. The MOS is 0.07.

Algae

The most sensitive endpoint was the NOEC (9.09 μg a.i./L), based on cell density and growth rates, for marine diatoms. The MOS is 0.12, thus, there is moderate risk to marine diatoms at the proposed maximum application rate of Tanos 50DF.

6.5 Risk mitigation

Based on the data submitted, an assessment of the environmental safety associated with the use of Tanos 50DF has identified the following mitigation measures:

- A freshwater aquatic buffer zone of 44 m is recommended when applying Tanos 50DF to potatoes and field tomatoes at the maximum application rate of 140–210 g a.i./ha (*Daphnia magna* chronic NOEC of 0.085 μg a.i./L, based on number of offspring produced; six applications at seven day intervals).
- A marine aquatic buffer zone of 23 m is recommended when applying Tanos 50DF to potatoes and field tomatoes at the maximum application rate of 140–210 g a.i./ha (mysid shrimp chronic NOEC of 0.83 μg famoxadone/L based on survival; six applications at seven day intervals).
- A run-off label statement is recommended.
- A bird, wild mammal and beneficial arthropods label statement is recommended.
- Environmental label statement suggestions and ammendments are listed in section 9.2.

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended use

Tanos 50DF is a dry flowable fungicide, containing famoxadone 25% and cymoxanil 25%, which is proposed for control of late blight and early blight of potatoes and field tomatoes. The proposed rates of application are 560 to 840 grams of product per hectare. By a.i., tghe proposed rates are:

Active Ingredient (a.i.)	Application Rate	
	gram product/ha	gram a.i./ha
famoxadone	280–420	140–210
cymoxanil	280–420	140–210

7.1.2 Mode of action

The Tanos 50DF formulated mixture offers modes of action that are complementary. They affect different and unrelated fungal target sites.

Famoxadone belongs to a new class of chemicals, the oxazolidinediones, which are part of the Quinone outside Inhibitors (QoI) fungicide group forming fungicide group 11. Famoxadone inhibits mitochondrial respiration at complex III (bc_1), specifically affecting the site of respiration enzyme ubiquinol:cytochrome c oxidoreductase. Famoxadone prevents sporangial differentiation, inhibits zoospore mobility and causes immediate lysis of zoospores in oomycetes. On non-oomycetes, it inhibits spore germination and mycelial growth.

Cymoxanil belongs to fungicide group 27. It is an inhibitor of multiple cellular processes including: nucleic acid synthesis, mycelial respiration, membrane permeability and inhibition of amino acid biosynthesis. It is metabolized by sensitive fungi into toxic metabolites. Cymoxanil has contact and local systemic activity. It works by three modes of action: preventive, curative and sporulation-inhibitive. Cymoxanil is known to penetrate into the foliage of treated crops. It is also known to be locally systemic; it redistributes within the leaf and allows compensation for incomplete foliage coverage. It can move acropetally in the xylem tissue but has little or no downward movement. It has been demonstrated that uptake and translocation of cymoxanil can be enhanced when it is applied in mixtures with other fungicides. When applied after infection occurs, cymoxanil is able to control disease progress curatively.

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7.1.3 Nature of the pest problem

Late blight (*Phytophthora infestans*)

Late blight, caused by *Phytophthora infestans*, is a highly destructive disease in potatoes and tomatoes. It survives mainly in abandoned potato and tomato plant material in fields, cull piles and gardens. All parts of the crops are susceptible. Symptoms resemble water-soaked spots, appearing first on the edges of lower leaves. Under moist condition the spots enlarge rapidly and form brown spots on leaves. A white ring appears on the border of the infected area and on the underside of the leaves. Under moist conditions, most of the above-ground parts of the plant rot away. In addition to blighting foliage, the fungus can infect potato tubers and tomato fruits. Affected tubers first show brownish blotch on the outer edge before harvest. The disease continues to develop after the crop is harvested, causing both the tomatoes and the potatoes to rot in storage. Late blight may result in total plant loss or death from early infection and severe reduction of the yield.

Early blight (*Alternaria solani*)

Early blight, caused by *Alternaria solani*, is one of the most common diseases in the world. It survives between crops mainly in diseased plant debris in the soil, in potato tubers, or in other crops and weeds. The early blight fungus can be seed-borne in tomatoes also. The relatively short cycle of *A. solani* allows for numerous, repeated infections, resulting in rapid defoliation under favourable conditions. The leaf spots are dark brown to black in colour, shaped in a ring that enlarges over time. Lower leaves are usually attacked first, then the disease progresses upward, resulting in yellow leaves that dry up or fall off, or both. Stem lesions developing on the seedlings can develop cankers, which girdle the stem, causing death of the plant. Under conditions favourable for disease development, early blight can result in yield reductions of 20–30% in potatoes. Tuber infection and subsequent decay in storage can severely affect the quality of seed, fresh-market and processing potatoes. In tomatoes, early blight may cause severe defoliation with reduced fruit number and size. Fruits that are diseased frequently drop and losses of up to 50% of the immature fruit may occur.

7.1.4 Effectiveness against pest

Results were submitted from 60 field trials conducted in Canada and the U.S. between 1997 and 2000, to assess the performance of Tanos 50DF. In most trials, Tanos 50DF was compared with a commercial standard and an untreated check. Efficacy was assessed by rating percent foliage infection, percentage of defoliation, percentage of damage, area under the disease progress curve (AUDPC) and yield.

Late blight on potatoes

Forty-nine small-scale trials, conducted in 12 U.S. states and six provinces in Canada, were submitted to support this claim on potatoes. Adequate efficacy data conclusively support the proposed claim for control of late blight at 280 g a.i./ha under low disease pressure, 420 g a.i./ha under moderate to high disease pressure. The disease control was up to 100%, which was better than or equivalent to commercial standards.

Effect of product rates

The data fully support the proposed high rate when disease pressures are high. The data also showed that the proposed low rate provided adequate late blight control under low disease pressure.

Interval

Tanos 50DF was applied at 7 day intervals in most trials. The data showed that Tanos 50DF provided effective late blight control at 7-day intervals under high disease pressure.

Rainfastness

One study showed that Tanos 50DF provided adequate late blight control under a simulated heavy rainfall, started 12 hours after the application of Tanos 50DF. Another study showed that Tanos 50DF provided adequate late blight control after overhead irrigation began 24 hours after the application of Tanos 50DF. Data were not submitted to support the claim that Tanos 50DF penetrates into plant tissue within 2 hours after application. Therefore, only a claim of 12 hours rainfastness is acceptable.

The proposed use on potatoes for control of late blight is acceptable at the rate of 280–420 g a.i./ha (560–840 product/ha), applied at 7-day intervals. The rainfastness is 12 hours.

Early blight on potatoes

Thirty-one small-scale trials, conducted in 13 U.S. states and three provinces in Canada, were submitted to support the claim on potatoes. Adequate efficacy data conclusively support the proposed claim for control of early blight at 280 g a.i./ha under low disease pressure, 420 g a.i./ha under moderate to high disease pressure. The disease severity control was up to 100%, which was better than or equivalent to commercial standards.

Effect of product rates

The data fully support the proposed high rate when disease pressures are high. The data also showed that the proposed low rate provides adequate disease control under low disease pressure.

Interval

Tanos 50DF was applied at 7-day intervals in most trials. The data showed that Tanos 50DF provided effective early blight control at 7-day intervals under high disease pressure.

The proposed use on potatoes for control of early blight is acceptable at the rate of 280–420 g a.i./ha (560–840 product/ha), applied at 7-day intervals.

Late blight on Field Tomatoes

Five small-scale trials, conducted in three U.S. states, were submitted to support the claim on field tomatoes. One trial showed that Tanos 50DF provided adequate late blight control under high disease pressure. Three trials showed that Tanos 50DF provided adequate late blight control under low disease pressure. Tomato late blight is caused by *Phytophthora infestans*. The same pathogen responsible for potato late blight. The data from potatoes showed that Tanos 50DF was effective in controlling *Phytophthora infestans*. Therefore, the claim for control of late blight on field tomatoes is acceptable based on the limited field tomato data and the potato data.

Effect of product rates

The data support the proposed high rate (420 g a.i./ha) under high disease pressure. The data also show that the proposed low rate provides adequate late blight control under low disease pressure.

Interval

Tanos 50DF was applied at 7-day intervals in most trials. The data show that Tanos 50DF provided effective late blight control at 7-day intervals under high disease pressure.

The proposed use on tomatoes for control of late blight is acceptable at the rate of 280–420 g ai/ha (560–840 product/ha), applied at 7-day intervals.

Early blight on Field Tomatoes

Eleven small-scale trials, conducted in seven U.S. states, were submitted to support the claim on tomatoes.

Four trials showed that Tanos 50DF consistently provided adequate early blight control under high disease pressure at the proposed high rate. Two trials showed that Tanos 50DF provided adequate early blight control under low disease pressure. Tomato early blight is caused by *Alternaria solani*, the same pathogen responsible for potato early blight. The data from potatoes showed that Tanos 50DF was effective in controlling *Alternaria solani*. Therefore, the claim for control of early blight on field tomatoes is acceptable based on the limited field tomato data and the potato data.

Effect of product rates
The data support the proposed high rate (420 g a.i./ha) under high disease pressure. The data also show that the proposed low rate provides adequate disease control under low disease pressure.

Interval
Tanos 50DF was applied at 7-day intervals in most trials. The data showed that Tanos 50DF provided effective early blight control at 7-day intervals under high disease pressure.

The proposed use on field tomatoes for control of early blight is acceptable at the rate of 280–420 g a.i./ha (560–840 product/ha), applied at 7-day intervals.

7.2 Phytotoxicity to target plants (including different cultivars), or to target plant products

Sixteen potato and ten field tomato tolerance studies were submitted. Tanos 50DF was applied at the rates of 140, 210, 280 and 420 g a.i./ha (0.33× ,0.5×, 0.67×, and 1× the proposed high rate, respectively). Up to 10 applications were made, with a proposed maximum of six applications at the proposed high rate.

No crop injury or phytotoxicity was reported in any of the studies. Seventeen studies provided yield. Of these, 13 studies had higher yield after the application of Tanos 50DF.

7.3 Observations on undesirable or unintended side effects

No information was provided.

7.4 Economics

Not assessed

7.5 Sustainability

7.5.1 Survey of alternatives

The major alternative fungicide active ingredients currently registered for control of the pests on the proposed crops include, but are not necessarily limited to, the following:

Pest	Crop	Available alternative a.i.
Late blight	Potatoes	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), triazines (anilazine), phthalimides (captan), cinnamic acids (dimethomorph), acylalanines (metalaxyl-m), carbamates (propamocarb), dithio-carbamates (zineb, mancozeb, maneb, metiram), chloronitriles (chlorothalonil), cyanoacetamide oxime (cymoxanil), benzamides (zoxamide), methoxy-carbamates (pyraclostrobin)
Early blight	Potatoes	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), triazines (anilazine), phthalimides (captan), cinnamic acids (dimethomorph), acylalanines (metalaxyl-m), dithio-carbamates (zineb, mancozeb, maneb, metiram), chloronitriles (chlorothalonil), benzamides (zoxamide), methoxy-carbamates (pyraclostrobin)
Late blight	Tomatoes, field	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), triazines (anilazine), phthalimides (captan), dithio-carbamates (zineb, ziram, mancozeb, maneb, metiram), chloronitriles (chlorothalonil)
Early blight	Tomatoes, field	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), dithio-carbamates (zineb, ziram, mancozeb, maneb, metiram), phthalimides (captan), chloronitriles (chlorothalonil), triazines (anilazine), benzimidazoles (benomyl)

7.5.2 Compatibility with current management practices including Integrated Pest Management (IPM)

A number of disease management practices, in addition to chemical control, are available to growers of the target crops. For control of late blight and early blight on potatoes and field tomatoes, it is essential to employ early management strategies to minimize the introduction of inoculum into the field and to monitor blight development using disease prediction models relevant to the geography and regular field monitoring. As a foliar fungicide, Tanos 50DF is compatible with these practices.

7.5.3 Contribution to risk reduction

Tanos 50DF fits well into IPM strategies due to its strong activity on diseases. It is a potential alternative to some of the older fungicides currently used for control of the diseases in the target crops.

Pest	Crop	Available alternative a.i.
Late blight	Potatoes	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), triazines (anilazine), phthalimides (captan), cinnamic acids (dimethomorph), acylalanines (metalaxyl-m), carbamates (propamocarb), dithio-carbamates (zineb, mancozeb, maneb, metiram), chloronitriles (chlorothalonil), cyanoacetamide oxime (cymoxanil), benzamides (zoxamide), methoxy-carbamates (pyraclostrobin)
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Late blight	Tomatoes, field	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), triazines (anilazine), phthalimides (captan), dithio-carbamates (zineb, ziram, mancozeb, maneb, metiram), chloronitriles (chlorothalonil)
Early blight	Tomatoes, field	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), dithio-carbamates (zineb, ziram, mancozeb, maneb, metiram), phthalimides (captan), chloronitriles (chlorothalonil), triazines (anilazine), benzimidazoles (benomyl)

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7.5.4 Information on the occurrence or possible occurrence of the development of resistance

Tanos 50DF is a broad spectrum fungicide, containing famoxadone and cymoxanil. Famoxadone is a group 11 fungicide (QoI fungicide). Cymoxanil is a group 27 fungicide. Any fungal population may contain individuals naturally resistant to famoxadone and other group 11 fungicides and resistant to cymoxanil and other group 27 fungicides. The resistant biotypes may dominate the fungal population if group 11 and 27 fungicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to the site of action but are specific to individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance management strategies should be followed. Resistance management recommendations for Tanos 50DF will follow the QoI model fungicide since QoI fungicides have higher resistance risk than group 27 fungicides.

An appropriate resistance management section for group 11 fungicides has been developed in consultation with the North American QoI (NAQoI) Working Group for another QoI group fungicide, Headline, and will be used for Tanos 50DF.

GROUP	**11**	**27**	**FUNGICIDE**

7.6 Conclusion

For resistance management, this is a group 11 and 27 (famoxadone and cymoxanil) fungicide. Any fungal population may contain individuals naturally resistant to this product and other group 11 or 27 fungicides. The resistant biotypes may dominate the fungal population if these fungicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to the site of action but are specific to individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance management strategies should be followed.

To delay fungicide resistance:

1. Use a maximum of six applications per year.

2. Alternate with fungicides having a different mode of action other than those of groups 11 and 27 after each application of Tanos 50DF.

Table 1 Value summary

Crop/Pest	Recommendation (based on Value Assessment)	Comments
Potatoes		
Late blight	6 applications at 560–840 grams product/ha at 7-day intervals. Under lower to moderate disease infection, use the low rate. Under moderate to high infection, use the higher rate.	A maximum of 6 applications per year is recommended for resistance management. Alternate applications of Tanos 50DF with a non-QoI, non-group 27 fungicide having a different mode of action. Ground application only.
Early blight		
Tomatoes, field		
Late blight	6 applications at 560–840 grams product/ha at 7-day intervals. Under lower to moderate disease infection, use the low rate. Under moderate to high infection, use the higher rate.	A maximum of 6 applications per year is recommended for resistance management. Alternate applications of Tanos 50DF with a non-QoI, non-group 27 fungicide having a different mode of action. Ground application only.
Early blight		

8.0 Toxic Substances Management Policy (TSMP) considerations

During the review of famoxadone and the end-use product Tanos 50DF, the PMRA has taken into account the federal Toxic Substances Management Policy and has followed the Regulatory Directive DIR99-03. It has been determined that this product does not meet TSMP Track-1 criteria because:

Famoxadone does not meet the criteria for persistence. Its values for half-life in soil (38.3 days), water (0.4 days) and sediment (13.6 days) are below the TSMP Track-1 cut-off criteria for soil (≥ 182 days), water (≥ 182 days) and sediment (≥ 365 days). Because it is relatively non-volatile, a study for persistence in air was not triggered.

Famoxadone does not meet the criterion for bioacumulation. Studies have shown that the bioconcentration factor (BCF) of famoxadone is 3425 in whole fish, which is below the TSMP Track-1 cut-off criterion of BCF ≥ 5000. The octanol–water partition coefficient (log K_{ow}) is 4.65, which is below the TSMP Track-1 cut-off criterion of ≥ 5.0. Mammalian toxicology studies indicate that famoxadone does not accumulate in tissues and is excreted in feces and urine.

The toxicity of famoxadone is described in Chapters 3 and 6.

Table 1 Value summary

Crop/Pest	Recommendation (based on Value Assessment)	Comments
Potatoes		
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Early blight		
Tomatoes, field		
Late blight	6 applications at 560–840 grams product/ha at 7-day intervals. Under lower to moderate disease infection, use the low rate. Under moderate to high infection, use the higher rate.	A maximum of 6 applications per year is recommended for resistance management. Alternate applications of Tanos 50DF with a non-QoI, non-group 27 fungicide having a different mode of action. Ground application only.
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The toxicity of famoxadone is described in Chapters 3 and 6.

The major transformation products identified in the fate studies included IN-JS940, IN-H3310, IN-JL856, IN-MN968, IN-MN467, IN-MN468, IN-KF015 and IN-KZ007. Aerobic biotransformation studies with IN-KZ007 (DT_{50} = 1.5–10.3 days), IN-KF015 (DT_{50} = 1.2 days) and IN-JS940 (DT_{50} = 6–23 hours) indicated that these transformation products are not persistent in soil. Transformation products were not identified or quantified in the bioconcentration study in fish, however, depuration of the radiolabeled parent compounds was rapid with >90% of the accumulated residues eliminated by day 7. It is unlikely that these transformation products bioaccumulate and, therefore, they do not meet the TSMP Track-1 criteria.

Insufficient information is available to assess the transformation products IN-H3310, IN-JL856, IN-MN968, IN-MN467 and IN-MN468.

All formulants in Tanos 50DF are either on the USEPA List 3 or List 4. Famoxadone technical active contains xylene (0.1%) which is on the USEPA List 2. Xylene is not a known TSMP Track-1 substance, is an organic solvent with high volatility, and at the concentrations with which it will be present in the end-use product, should pose minimal risk to the environment.

Famoxadone (technical grade) does not contain any by-product or microcontaminant that meets the TSMP Track-1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.

9.0 Regulatory Decision

Famoxadone technical and its end-use product, Tanos 50DF (fungicide), containing famoxadone and the currently registered fungicide cymoxanil, have been granted temporary registration for the control of various fungal diseases on field tomatoes and potatoes, pursuant to Section 17 of the Pest Control Products Regulations, subject to the generation of the following data:

- in vivo dermal absorption
- method for enforcement
- octanol–water partition coefficients for major transformation products.

List of abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ARfD	acute reference dose
AST	aspartate aminotransferase
AUC	area under the curve
BrdU	5-bromo-2'-deoxyuridine
bw	body weight
bwg	body-weight gain
BWI	body weight per individual
CAS	Chemical Abstracts Service
d	day
DAP	days after planting
DAT	days after treatment
DF	dry flowable
CHO	Chinese Hamster Ovary
DEEM	Dietary Exposure Evaluation Model
DI	daily intake
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT_{50}	dissipation time (50%)
EC_{25}	effect concentration (25%)
EC_{50}	effect concentration (50%)
EEC	expected environmental concentration
EP	end-use product
F	female
F_0	parental animals
F_1	first generation offspring
F_2	second generation offspring
FC	food consumption
FOB	functional observational battery
FT_4	free thyroxine
GAP	good agricultural practices
GC	gas chromatography
h	hour
ha	hectare
HAFT	highest average field trial
Hb	hemoglobin
Hct	hematocrit
HPLC	high-performance liquid chromatography
ILV	independent laboratory validation
K_d	Freundlich adsorption coefficient (ratio of concentration in the soil phase to that in the aqueous phase, under test conditions)

kg	kilogram
K_{oc}	organic carbon adsorption coefficient (relates K_d to the organic carbon content of the soil sample)
K_{ow}	octanol–water partition coefficient
LC	liquid chromatography
LC_{50}	lethal concentration (50%)
LD_{50}	lethal dose (50%)
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
LOQ	limit of quantitation
M/F	male/female
M	male
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MS	mass spectrometry
MSD	mass selective detection
n	number of trials
nm	nanometers
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand White
OM	organic matter
Pa	pascal
PDI	potential daily intake
PHED	Pesticide Handlers' Exposure Database
PHI	pre-harvest interval
ppm	parts per million
QoI	quinone outside inhibition
RAC	raw agricultural product
RBC	red blood cells
REI	re-entry interval
ROC	residue of concern
RP	reverse phase
SD	Sprague-Dawley
SD	standard deviation
SF	safety factor
T_3	tri-iodothyronine
T_4	thyroxine
TRR	total radioactive residue
UDS	unscheduled DNA synthesis
UV	ultraviolet
WG	wettable granules
WDG	water dispersible granules

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Appendix I Toxicology

Metabolism of Rat: The fate of DPX-JE874 was investigated in male and female rats after single oral administration of U-^{14}C-phenylamino-famoxadone at dose levels of 5 or 100 mg/kg bw or at 5 mg/kg bw following 14 consecutive daily doses of nonradiolabeled famoxadone at 5 mg/kg bw. In addition, U-^{14}C phenoxyphenyl-famoxadone was administered as a single oral dose of 100 mg/kg bw. In a supplemental study, bile-duct cannulated rats were administered a single oral dose of either ^{14}C-phenylamino- or ^{14}C-phenoxyphenyl- (PA or POP) labeled famoxadone at 5 mg/kg bw.

The rate of absorption: The total recovery of the administered radioactivity was 94.6–103.1% from the various dose groups using normal rats and 94.3–103.5% from the bile-duct cannulated rats. Famoxadone was rapidly absorbed from the G.I. tract, but absorption appeared to be limited. Maximum concentrations of radioactivity in plasma were observed within 4 hours for the low dose and within 12 hours for the high dose. Based on the recovery of the radioactivity in the urine, bile and tissues of the bile-duct cannulated rats, 37–41% of the dose was absorbed by rats following a low dose; therefore, 59–63% of the dose was not absorbed. There were generally no sex-related or ^{14}C-label differences in the concentration of radioactivity in plasma. Plasma Area Under the Curve (AUC) values were also similar between ^{14}C-labels and sexes with the exception of high dose (PA) in which plasma AUC values were 1.7× higher in males than in females.

Distribution: There was no indication of ^{14}C-residues accumulating in tissues. The relative distribution of radioactivity among tissues was similar regardless of sex and dose level. For the [^{14}C-PA]-dosed groups the highest concentrations of radioactivity were in liver, fat and adrenals at the initial sampling intervals. Tissue concentrations of radioactivity in the high-dose [^{14}C-POP] rats were similar between the sexes, but differed from the equivalent high-dose [^{14}C-PA] group. By 120 hours post-dose, the highest radioactivity concentrations were in fat, bone marrow and adrenals.

Excretion: For each dose group, radioactivity was eliminated primarily in the feces, with the majority of excretion occurring within 24 hours of dosing. The pattern of excretion was similar regardless of sex, ^{14}C-label position, dose level, or pretreatment. In each group, radioactivity recovered in the feces accounted for 87.1–95.8% of the dose and radioactivity in the urine accounted for 2.9–11.7% of the dose. Radioactivity remaining in the tissues and residual carcass by 120 hours post-dose accounted for 0.04–0.73% of the dose. Data from the bile-duct cannulated rats indicated that biliary excretion at the low-dose level accounted for 29.8–38.6% of the administered dose.

Metabolism: Unchanged parent compound was the major component identified in fecal extracts from all dose groups accounting for 50.9–83.6% of the dose. The hydroxylated metabolites IN-KZ534 (0.5–13.4% dose) and IN-KZ007 (1.0–13.0% dose) were also identified in fecal extracts from all dose groups. The metabolite 4-acetoxyaniline (1.9–8.3% dose) was identified only in urine of [^{14}C-PA]-dosed rats and the metabolite IN-KZ000 (1.2–2.2% dose) was identified only in urine of [^{14}C-POP]-dosed rats. Only parent compound (29.8–52.6% of the dose) was detected in fecal extracts from bile-duct cannulated rats. Eight metabolites were identified in bile following enzymatic hydrolysis with β-glucuronidase/sulfatase. The bile metabolite profile was similar between the sexes. For the [^{14}C-PA]-dosed rats, the major components in bile were identified as conjugates of IN-KZ007 (2.6–3.4% dose) and catechol (2.7–4.6% dose), along with conjugates of IN-KZ532, IN-KZ534 and IN-ML815 (each at ≤1.8% dose). In the [^{14}C-POP]-dosed rats, the major components in bile were identified as conjugates of IN-KZ007 (1.4–5.1% dose) and IN-ML436 (3.5–3.6% dose), along with conjugates of IN-KZ532, IN-KZ000, IN-KZ534, IN-MN967 and IN-ML815 (each at ≤1.7% dose).

Metabolism of Dog: [U-^{14}C-phenylamino]-famoxadone was administered to male beagle dogs as a single oral gavage dose at 15 mg/kg body weight.

The rate of absorption was rapid; however, absorption appeared to be limited. The radioactivity peaked by 2 hours post-dose in plasma and by 4 hours post-dose in red blood cells and then declined steadily. The terminal half-life of elimination was 67–75 hours from plasma and 146–59 hours from the red blood cell.

Distribution: At 2 hours post-dose the highest concentrations of radioactivity were in liver, mesenteric fat, plasma, red blood cells, eye and aqueous humor. Radioactivity remaining in tissues at 96 hours post-dose accounted for 0.24% of the dose.

Excretion: This occurred primarily in the feces from 0–24 hours post-dose (61.7% dose) and was essentially complete within 96 hours of dosing. Total radioactivity in the feces was 70.3% and 7.7% in urine.

Metabolism: The biotransformation involves hydroxylation of parent to form KZ007 or KZ532, or opening of the oxazolidinedione ring to form JL856. Subsequently, hydroxylation or ring opening of metabolites produce KZ534 or ML815. Analyses of extracts from feces collected 0–24 hours post-dose (61.7% dose) indicated that parent was initially the major component in feces, accounting for 93.7–97.1% of the radioactivity. At longer post-dose intervals (24–96 hours; 8.6% of the dose), fecal extracts contained the metabolites KZ007 (21.4–33.4%) and ML815 (3.7–9.1%), along with relatively lower levels of parent (11.6–34.8%). Analyses of urine samples (0–96 hours) isolated up to eight unknown regions of radioactivity. Parent was not detected in urine and each of the isolated unknown components accounted for <2% of the dose. Enzymatic hydrolysis of urine (0–12 hour) with β-glucuronidase and sulfatase did not release any known metabolite. Analyses of liver extracts detected parent (40.4%) and KZ007 (9.7%) and analyses of fat extracts detected nearly all parent (97.4%) along with minor amounts of KZ007 (1.0%). Analyses of plasma detected parent (9.8%), ML815 (14.6%) and KZ007/JL856 (18.8%) and analyses of red blood cells detected parent (16.5%) and the metabolites ML815, KZ007 and JL856, together accounting for 3.6% of the extracted radioactivity.

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Acute Studies			
Oral	Rat—Crl:CD BR 5/sex; 5000 mg/kg bw	$LD_{50} > 5000$ mg/kg	**Low Toxicity**
Oral (spray dried granule formulation containing 500g/kg of a.i.)	Rat—SD, 5/sex; 5000 mg/kg bw	$LD_{50} > 5000$ mg/kg Males 3100 mg/kg Females	Clinical signs of toxicity included lethargy, immobility, low or hunched over posture, ocular discharge, wet or stained underbody or perineum, or diarrhea, spasms, tremors, ruffled fur, irregular respiration, lung noise, alopecia and stained nose, head, or face. **Low Toxicity**
Dermal	Rabbit—NZW, 5/sex; 2000 mg/kg	$LD_{50} > 2000$ mg/kg	**Low Toxicity**
Inhalation	Rat—Crl:CD BR, 5/sex/dose; 1.39 and 4.65 mg/L	$LC_{50} > 5.3$ mg/L MMAD = 4.7 μm GSD = 2.0 μm	Clinical signs included compound-stained facial fur, nasal discharge, stained perineum, ocular discharge, diarrhea and hunched posture. **Low Toxicity**
Skin Irritation	Rabbit—NZW, 6 females 0.5 g dose	MIS = 1.0 at 24 hours MAS = 0.61 (24, 48 and 72 hr)	**Slightly Irritating**
Eye Irritation	Rabbit—NZW; 6 females 20 mg dose	MIS = 7.0 at 1 hour MAS = 1.2 (24, 48 and 72 hr)	Conjunctival irritation in all rabbits up to and including 48 hours **Minimally Irritating**
Skin Sensitization (Maximization method)	Guinea pig—Hartley; 10 males in test group and naive control; 6 males for positive control. 100 and 30% for induction and 33% for challenge.	Test material gave a negative sensitization response. Positive control gave a positive response, showing the responsiveness of the assay.	**Not a Skin Sensitizer**

Study	**Species/Strain and Doses**	**NOEL/NOAEL and LOEL mg/kg bw/day**	**Target Organ/Significant Effects/Comments**
Acute Studies—Formulation (Tanos 50WG EP)			
Oral	Rat—Crl:CD (SD) BR albino, 5/sex; 100, 3000, 4000, 5000 mg/kg bw	LD$_{50}$ = 1732mg/kg bw, Males 566mg/kg bw, Females 1311mg/kg bw, combined	Clinical signs of toxicity observed in both sexes included lethargy, hunched over posture, ruffled fur, tremors, ataxia, abnormal gait or mobility, exophthalmus and low posture, external staining (nose or face), low or high carriage, moribundity, immobility, splayed legs, sore toe, convulsions, weakness, clear ocular discharge, dark eyes and irregular respiration. **Moderately toxic**
Dermal	Rat—Crl:CD (SD) BR albino, 5/sex; 5000 mg/kg	LD$_{50}$ > 5000 mg/kg	**Low Toxicity**
Inhalation	Rat—Crl:CD (SD) BR albino, 5/sex; 5.1 mg/L	LC$_{50}$ >5.1 mg/kg bw	**Low Toxicity**
Skin Irritation	Rabbit—NZW, 6 females 0.5 g dose	MIS = 0.33 at 24 hours MAS = 0.25 (24, 48 and 72 hr)	**Minimally Irritating**
Eye Irritation	Rabbit—NZW; 6 females 63 mg dose	MIS = 18.5 of 110 at 1 hour (unwashed eye) MAS 2.2 of 110 mean at 24, 48 and 72 hr	**Mildly irritating** **CAUTION: EYE IRRITANT**
Skin Sensitization Buehler Method	Guinea Pig—Hartley, 100% both induction and challenge phase Negative control: 0.9% saline Positive control	Not a skin sensitizer	**Not a skin sensitizer**

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Acute Studies			
Oral	Rat—Crl:CD BR 5/sex; 5000 mg/kg bw	LD_{50} > 5000 mg/kg	**Low Toxicity**
Oral (spray dried granule formulation containing 500g/kg of a.i.)	Rat—SD, 5/sex; 5000 mg/kg bw	LD_{50} > 5000 mg/kg Males 3100 mg/kg Females	Clinical signs of toxicity included lethargy, immobility, low or hunched over posture, ocular discharge, wet or stained underbody or perineum, or diarrhea, spasms, tremors, ruffled fur, irregular respiration, lung noise, alopecia and stained nose, head, or face. **Low Toxicity**
Dermal	Rabbit—NZW, 5/sex; 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low Toxicity**
Inhalation	Rat—Crl:CD BR, 5/sex/dose; 1.39 and 4.65 mg/L	LC_{50} > 5.3 mg/L MMAD = 4.7 μm GSD = 2.0 μm	Clinical signs included compound-stained facial fur, nasal discharge, stained perineum, ocular discharge, diarrhea and hunched posture. **Low Toxicity**
Skin Irritation	Rabbit—NZW, 6 females 0.5 g dose	MIS = 1.0 at 24 hours MAS = 0.61 (24, 48 and 72 hr)	**Slightly Irritating**
Eye Irritation	Rabbit—NZW; 6 females 20 mg dose	MIS = 7.0 at 1 hour MAS = 1.2 (24, 48 and 72 hr)	Conjunctival irritation in all rabbits up to and including 48 hours **Minimally Irritating**
Skin Sensitization (Maximization method)	Guinea pig—Hartley; 10 males in test group and naive control; 6 males for positive control. 100 and 30% for induction and 33% for challenge.	Test material gave a negative sensitization response. Positive control gave a positive response, showing the responsiveness of the assay.	**Not a Skin Sensitizer**

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Acute Studies—Formulation (Tanos 50WG EP)			
Oral	Rat—Crl:CD (SD) BR albino, 5/sex; 100, 3000, 4000, 5000 mg/kg bw	LD_{50} = 1732mg/kg bw, Males 566mg/kg bw, Females 1311mg/kg bw, combined	Clinical signs of toxicity observed in both sexes included lethargy, hunched over posture, ruffled fur, tremors, ataxia, abnormal gait or mobility, exophthalmus and low posture, external staining (nose or face), low or high carriage, moribundity, immobility, splayed legs, sore toe, convulsions, weakness, clear ocular discharge, dark eyes and irregular respiration. **Moderately toxic**
Dermal	Rat—Crl:CD (SD) BR albino, 5/sex; 5000 mg/kg	LD_{50} > 5000 mg/kg	**Low Toxicity**
Inhalation	Rat—Crl:CD (SD) BR albino, 5/sex; 5.1 mg/L	LC_{50} >5.1 mg/kg bw	**Low Toxicity**
Skin Irritation	Rabbit—NZW, 6 females 0.5 g dose	MIS = 0.33 at 24 hours MAS = 0.25 (24, 48 and 72 hr)	**Minimally Irritating**
Eye Irritation	Rabbit—NZW; 6 females 63 mg dose	MIS = 18.5 of 110 at 1 hour (unwashed eye) MAS 2.2 of 110 mean at 24, 48 and 72 hr	**Mildly irritating** **CAUTION: EYE IRRITANT**
Skin Sensitization Buehler Method	Guinea Pig—Hartley, 100% both induction and challenge phase Negative control: 0.9% saline Positive control	Not a skin sensitizer	**Not a skin sensitizer**

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
28-day dermal, rat	Rat—Crl:CD (BR), 10/sex/dose 0, 250, 500, or 1000 mg/kg bw/day, 5 days/week (4 mL/kg bw)	**Systemic toxicity** NOAEL = 250/1000 mg/kg bw/day (M/F) LOAEL = 500 mg/kg bw/day (M) **Dermal toxicity** NOAEL = 1000 mg/kg bw/day (M&F)	≥500 and 1000 mg/kg/day : increased alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase; increased liver weights and relative brain weight. Increased incidence of the following mild grade hepatic lesions—apoptosis, centrilobular hepatocyte hypertrophy, mitotic figures (M), increased liver weights and liver hepatocellular hypertrophy—are considered to be an adaptive response. No compound-related effect was observed in the females.
90-day, mouse (diet)	Mouse—Crl:CD (BR) 20/sex/dose 0, 35, 350, 3500, 7000 ppm (0/0, 5.89/8.21, 62.4/79.7, 534/757, 1149/1552 mg/kg bw/day, M/F)	NOAEL = 350 ppm (M/F) (62.4/79.9 mg/kg bw/day, M/F) LOAEL = 3500 ppm (M/F) (534/757 mg/kg bw/day, M/F)	≥3500 ppm: main study; increased absolute and relative liver weights (M&F), hepatic lesions; single cell necrosis, bile pigment, centrilobular hypertrophy and diffuse fatty change (M&F), minimal focal liver necrosis (M) Satellite study (2-week sacrifice): increase in absolute and relative liver weights (M&F); increased hepatic β-oxidation activity and increase in total cytochrome P-450 content (M&F) Mild hemolytic anemia, lower hemoglobin, reticulocytes and mean corpuscular hemoglobin concentration [M&F], increased mean corpuscular volume and mean corpuscular hemoglobin (F), decreased platelets (M&F), higher leukocytes and lymphocytes (F), increased absolute and relative spleen weights and greater incidence of red pulp (F), higher hemosiderin in spleen (M&F) 7000 ppm: greater absolute and relative spleen weights and incidence of red pulp in the spleen (M), lower erythrocytes (F), higher mean corpuscular volume and mean corpuscular hemoglobin (M), increased neutrophils and decreased eosinophils (F), greater incidence of minimal atrophy of the caudate lobe of the liver (F)

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
90-day, rat (diet)	Rat—Crl:CD(BR) 10/sex/dose 0. 50, 200, 800, 1600 ppm (M/F) 0/0, 3.34/4.24, 13.0/16.6, 52.1/65.7, 106/130 mg/kg bw/day, (M/F)	NOAEL = 50 ppm (M/F) 3.34/4.24 mg/kg bw (M/F) LOAEL = 200 ppm (M/F) 13.0/16.6 mg/kg bw/day (M/F)	≥200 ppm: decreased erythrocytes, hemoglobin, (M&F), lower glucose (M), decreased bwg, globulin, hematocrit, food consumption and food efficiency (F), higher mean corpuscular volume, relative liver weight and peroxisomal β-oxidation rate (F) ≥800 ppm: lower RBC, hemoglobin, hematocrit, reticulocytes, higher mean corpuscular volume, mean corpuscular hemoglobin and total protein, greater spleen weight absolute (F) and relative (M&F), greater incidence of bone marrow hyperplasia, spleen congestion, extramedullary hematopoiesis and hemosiderin (M&F); increased liver weights (F), focal degeneration, bile duct hyperplasia (M), centrilobular hypertrophy; increased mitotic figures, apoptosis, (M&F); increased alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase (M), higher sorbitol dehydrogenase (M&F), lower glucose (F), increase in peroxisomal β-oxidation rate in the liver (M&F), higher BrdU labeling index in liver (M) 1600 ppm: liver discolouration (M), higher bilirubin (M&F), higher cholesterol and lower glucose (F), increased leucocytes, lymphocytes, meutrophils (M), greater bile pigment (M&F), increased absolute spleen weight (M), higher BrdU labeling index in liver (F)

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
28-day dermal, rat	Rat—Crl:CD (BR), 10/sex/dose 0, 250, 500, or 1000 mg/kg bw/day, 5 days/week (4 mL/kg bw)	**Systemic toxicity** NOAEL = 250/1000 mg/kg bw/day (M/F) LOAEL = 500 mg/kg bw/day (M) **Dermal toxicity** NOAEL = 1000 mg/kg bw/day (M&F)	≥500 and 1000 mg/kg/day : increased alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase; increased liver weights and relative brain weight. Increased incidence of the following mild grade hepatic lesions—apoptosis, centrilobular hepatocyte hypertrophy, mitotic figures (M), increased liver weights and liver hepatocellular hypertrophy—are considered to be an adaptive response. No compound-related effect was observed in the females.
90-day, mouse (diet)	Mouse—Crl:CD (BR) 20/sex/dose 0, 35, 350, 3500, 7000 ppm (0/0, 5.89/8.21, 62.4/79.7, 534/757, 1149/1552 mg/kg bw/day, M/F)	NOAEL = 350 ppm (M/F) (62.4/79.9 mg/kg bw/day, M/F) LOAEL = 3500 ppm (M/F) (534/757 mg/kg bw/day, M/F)	≥3500 ppm: main study; increased absolute and relative liver weights (M&F), hepatic lesions; single cell necrosis, bile pigment, centrilobular hypertrophy and diffuse fatty change (M&F), minimal focal liver necrosis (M) Satellite study (2-week sacrifice): increase in absolute and relative liver weights (M&F); increased hepatic β-oxidation activity and increase in total cytochrome P-450 content (M&F) Mild hemolytic anemia, lower hemoglobin, reticulocytes and mean corpuscular hemoglobin concentration [M&F], increased mean corpuscular volume and mean corpuscular hemoglobin (F), decreased platelets (M&F), higher leukocytes and lymphocytes (F), increased absolute and relative spleen weights and greater incidence of red pulp (F), higher hemosiderin in spleen (M&F) 7000 ppm: greater absolute and relative spleen weights and incidence of red pulp in the spleen (M), lower erythrocytes (F), higher mean corpuscular volume and mean corpuscular hemoglobin (M), increased neutrophils and decreased eosinophils (F), greater incidence of minimal atrophy of the caudate lobe of the liver (F)

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
90-day, rat (diet)	Rat—Crl:CD(BR) 10/sex/dose 0, 50, 200, 800, 1600 ppm (M/F) 0/0, 3.34/4.24, 13.0/16.6, 52.1/65.7, 106/130 mg/kg bw/day, (M/F)	NOAEL = 50 ppm (M/F) 3.34/4.24 mg/kg bw (M/F) LOAEL = 200 ppm (M/F) 13.0/16.6 mg/kg bw/day (M/F)	≥200 ppm: decreased erythrocytes, hemoglobin, (M&F), lower glucose (M), decreased bwg, globulin, hematocrit, food consumption and food efficiency (F), higher mean corpuscular volume, relative liver weight and peroxisomal β-oxidation rate (F) ≥800 ppm: lower RBC, hemoglobin, hematocrit, reticulocytes, higher mean corpuscular volume, mean corpuscular hemoglobin and total protein, greater spleen weight absolute (F) and relative (M&F), greater incidence of bone marrow hyperplasia, spleen congestion, extramedullary hematopoiesis and hemosiderin (M&F); increased liver weights (F), focal degeneration, bile duct hyperplasia (M), centrilobular hypertrophy; increased mitotic figures, apoptosis, (M&F); increased alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase (M), higher sorbitol dehydrogenase (M&F), lower glucose (F), increase in peroxisomal β-oxidation rate in the liver (M&F), higher BrdU labeling index in liver (M) 1600 ppm: liver discolouration (M), higher bilirubin (M&F), higher cholesterol and lower glucose (F), increased leucocytes, lymphocytes, meutrophils (M), greater bile pigment (M&F), increased absolute spleen weight (M), higher BrdU labeling index in liver (F)

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
90-day, dog (diet)	Beagle dog 4/sex/group 0, 40, 300, or 1000/600 ppm (600 ppm from study day 37–90) (0/0, 1.3/1.4, 10.0/10.1, or 23.8/23/[21.2/20.0]mg/kg bw/day, M/F)	NOAEL= 40 ppm (M) (1.3 mg/kg bw/day) NOAEL for females was not established LOAEL=300/40 ppm (M/F) (10.0/1.4 mg/kg bw/day, M/F)	≥40 ppm: one F had microscopic lens lesion (lenticular cataracts and microscopic lens lesions consisting of a small focal zone of swollen lens fibres at the Y suture of the posterior lens capsule, decreased erythrocytes, hemoglobin and hematocrit (F) ≥300 ppm: decreased erythrocytes, hemoglobin, hematocrit, increased MCV (M&F), greater incidence of lenticular cataracts and microscopic lens lesions consisting of a small focal zone of swollen lens fibres at the Y suture of the posterior lens capsule (M) At 40 ppm (F) and 300 ppm (M&F) this anemic condition was minor and the biological relevance was equivocal. 1000/600 ppm: myotonic twitches were first observed approximately 4 hours following feeding on Day 21 and thereafter the twitches were regularly observed throughout the study (M&F), one 1000 ppm female had convulsions and ataxia on Day 34. Soft stools, decreased defecation and diarrhea in F, lower bw/bwg, food consumption and food efficiency (M&F), higher serum potassium (M&F), lower absolute and relative testes weight and epididymides and bilateral immature seminiferous tubules These effects were considered equivocal since decreases in testes weight and epidymides sometimes occur in dogs when bw is suppressed before the dogs reach sexual maturation.

Study	**Species/Strain and Doses**	**NOEL/NOAEL and LOEL mg/kg bw/day**	**Target Organ/Significant Effects/Comments**
Short-term Toxicity			
52-week, dog (diet)	Beagle dog 4/sex/group 0, 10, 20, 40, or 300 ppm (0/0,0.3/0.3, 0.6/0.6, 1.2/1.2, or 8.8/9.3 mg/kg bw/day) Recovery group: 300 ppm for 3 months and basal diet for 9 months	NOAEL not determined LOAEL not determined due to artifact observed at all dose levels	300 ppm: ocular lesions (microscopically posterior and equatorial subcapsular lens cataracts, microscopically lenticular degeneration of the posterior cortex and/or equatorial fibres in the 300 ppm treatment groups and the 300 ppm recovery groups. The lesions were characterized by fibre swelling with the formation of Morgagnian globules and clefts within the lens cortex. Lesions were most common in the posterior subcapsular cortex with variable extensions into the deeper cortex. Changes in the equatorial fibres were less common and only observed in the 300 ppm treated groups. Cataracts may have also occurred at lower dose(s),but microscopic slides of eyes were of inadequate diagnostic quality due to fixation artifacts. Limited regression of cataracts in Recovery Group at 12 months. No other adverse effect observed in M or F.
52-week, monkey (gavage)	Cynomolgus monkey 4/sex/group 0, 1, 100, or 1000 mg/kg bw/day	NOAEL = 100 mg/kg bw/day LOAEL = 1000 mg/kg bw/day	1000 mg/kg bw/day: mild hemolytic anemia (decreased erythrocytes, hemoglobin and hematocrit) and secondary microscopic effects in the liver, spleen and kidney (increased blood pigments and splenic sinus dilatation), M&F
Chronic Toxicity and Oncogenicity			
18-month, mouse (diet)	Crl:CD-1(IRC)BR mice 80/sex/group 0, 5, 50, 700 or 2000 ppm (0/0, 0.70/0.96, 6.8/9.8, 96/130, or 274/392, M/F)	NOAEL = 700 ppm (M/F) (96/130 mg/kg bw/day, M/F) LOAEL = 2000 ppm (M/F) (27.4/392 mg/kg bw/day, M/F) **No carcinogenicity**	2000 ppm: greater mortality from amyloidosis, increased liver weight, slight hepatotoxicity, including focal necrosis, diffuse fatty change (M), liver discolouration, greater Kupffer cell lipofuscin pigment (M&F), higher incidence of amyloidosis and apoptosis (F)

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
90-day, dog (diet)	Beagle dog 4/sex/group 0, 40, 300, or 1000/600 ppm (600 ppm from study day 37–90) (0/0, 1.3/1.4, 10.0/10.1, or 23.8/23/[21.2/20.0]mg/kg bw/day, M/F)	NOAEL= 40 ppm (M) (1.3 mg/kg bw/day) NOAEL for females was not established LOAEL=300/40 ppm (M/F) (10.0/1.4 mg/kg bw/day, M/F)	≥40 ppm: one F had microscopic lens lesion (lenticular cataracts and microscopic lens lesions consisting of a small focal zone of swollen lens fibres at the Y suture of the posterior lens capsule, decreased erythrocytes, hemoglobin and hematocrit (F) ≥300 ppm: decreased erythrocytes, hemoglobin, hematocrit, increased MCV (M&F), greater incidence of lenticular cataracts and microscopic lens lesions consisting of a small focal zone of swollen lens fibres at the Y suture of the posterior lens capsule (M) At 40 ppm (F) and 300 ppm (M&F) this anemic condition was minor and the biological relevance was equivocal. 1000/600 ppm: myotonic twitches were first observed approximately 4 hours following feeding on Day 21 and thereafter the twitches were regularly observed throughout the study (M&F), one 1000 ppm female had convulsions and ataxia on Day 34. Soft stools, decreased defecation and diarrhea in F, lower bw/bwg, food consumption and food efficiency (M&F), higher serum potassium (M&F), lower absolute and relative testes weight and epididymides and bilateral immature seminiferous tubules These effects were considered equivocal since decreases in testes weight and epidymides sometimes occur in dogs when bw is suppressed before the dogs reach sexual maturation.

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Short-term Toxicity			
52-week, dog (diet)	Beagle dog 4/sex/group 0, 10, 20, 40, or 300 ppm (0/0,0.3/0.3, 0.6/0.6, 1.2/1.2, or 8.8/9.3 mg/kg bw/day) Recovery group: 300 ppm for 3 months and basal diet for 9 months	NOAEL not determined LOAEL not determined due to artifact observed at all dose levels	300 ppm: ocular lesions (microscopically posterior and equatorial subcapsular lens cataracts, microscopically lenticular degeneration of the posterior cortex and/or equatorial fibres in the 300 ppm treatment groups and the 300 ppm recovery groups. The lesions were characterized by fibre swelling with the formation of Morgagnian globules and clefts within the lens cortex. Lesions were most common in the posterior subcapsular cortex with variable extensions into the deeper cortex. Changes in the equatorial fibres were less common and only observed in the 300 ppm treated groups. Cataracts may have also occurred at lower dose(s),but microscopic slides of eyes were of inadequate diagnostic quality due to fixation artifacts. Limited regression of cataracts in Recovery Group at 12 months. No other adverse effect observed in M or F.
52-week, monkey (gavage)	Cynomolgus monkey 4/sex/group 0, 1, 100, or 1000 mg/kg bw/day	NOAEL = 100 mg/kg bw/day LOAEL = 1000 mg/kg bw/day	1000 mg/kg bw/day: mild hemolytic anemia (decreased erythrocytes, hemoglobin and hematocrit) and secondary microscopic effects in the liver, spleen and kidney (increased blood pigments and splenic sinus dilatation), M&F
Chronic Toxicity and Oncogenicity			
18-month, mouse (diet)	Crl:CD-1(IRC)BR mice 80/sex/group 0, 5, 50, 700 or 2000 ppm (0/0, 0.70/0.96, 6.8/9.8, 96/130, or 274/392, M/F)	NOAEL = 700 ppm (M/F) (96/130 mg/kg bw/day, M/F) LOAEL = 2000 ppm (M/F) (27.4/392 mg/kg bw/day, M/F) **No carcinogenicity**	2000 ppm: greater mortality from amyloidosis, increased liver weight, slight hepatotoxicity, including focal necrosis, diffuse fatty change (M), liver discolouration, greater Kupffer cell lipofuscin pigment (M&F), higher incidence of amyloidosis and apoptosis (F)

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
24-month, rat (diet)	Rat—Crl:CD (BR) 92/sex/group 0, 10, 40, 200, or 400 ppm (0/0, 0.4/0.5, 1.6/2.2, 8.4/10.7, or 16.8/23.0 mg/kg bw/day, M/F)	NOAEL = 200/40 ppm (8.4/2.2, M/F) LOAEL = 400/200 ppm (M/F) (16.8/10.7 mg/kg bw/day, M/F) **No carcinogenicity**	200 ppm, F: lower bwg and food efficiency, slight hemolytic anemia (lower erythrocytes, hemoglobin, hematocrit, mean corpuscular volume) 400 ppm, M: slight hemolytic anemia (lower RBC, greater reticulocyte, mean corpuscular volume and mean corpuscular hemoglobin) with compensatory erythropoiesis and microscopic changes in the liver (focal cystic degeneration, focal hepatocellular degeneration and eosinopholic foci of cellular alterations, apoptosis) F-liver discolouration, increased Kupffer cell pigmentation (hemosiderin) and centrilobular hypertrophy at 1-year sacrifice and apoptosis, focal hepatocellular degeneration and centrilobular hypertrophy at 2-year sacrifice
Reproduction and Developmental Toxicity			
2-generation, rat (1litter/generation)	Rat— Crl:CD(BR) 30/sex/group 0, 20, 200, or 800 ppm (0/0, 1.1/1.5, 11.3/14.2, or 44.7/53.3 mg/kg bw/day, M/F)	**Maternal** NOAEL = 200 ppm (11.3/14.2 mg/kg bw/day, M/F) LOAEL = 800 ppm (44.7/53.3 mg/kg bw/day, M/F) **Offspring** NOAEL = 200 ppm (11.3/14.2 mg/kg bw/day, M/F) LOAEL = 800 ppm (44.7/53.3 mg/kg bw/day, M/F) **Reproductive** NOAEL = 800 ppm (44.7/53.3 mg/kg bw/day, M/F) LOAEL not observed	800 ppm: decreased bw/bwg and food consumption (M&F), hepatotoxicity (increased liver weights, higher alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, bilirubin, cholesterol, deacreased triglycerides, liver foci, discolouration, focal fatty changes, eosiniphilic focus and cellular alteration) 800 ppm: lower pup bw (both F_1 and F_2).

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Developmental, rat	Rat—Crl:CD(BR) 25/group 0, 125, 250, 500, or 1000 mg/kg bw/day	**Maternal** NOAEL = 250 mg/kg bw/day LOAEL = 500 mg/kg bw/day **Developmental** NOAEL = 1000 mg/kg bw/day (limit dose) LOAEL not estimated **No teratogenic potential**	≥500 mg/kg bw: transient decrease in bw/bwg and food consumption
Developmental, rabbits	Hra:NZW SPF rabbits 20/group 0, 100, 350, or 1000 mg/kg bw/day	**Maternal** NOAEL = 350 mg/kg bw/day LOAEL = 1000 mg/kg bw/day **Developmental** NOAEL = 350 mg/kg bw/day LOAEL = 1000 mg/kg bw/day No teratogenic potential	1000 mg/kg bw: more abortion, decreased bw/bwg and food consumption, higher number of does with abnormal or little or no stool 1000 mg/kg bw: more abortion Since it cannot be determined whether the abortions (4 of 17) are due to maternal toxicity or developmental toxicity (or both), these abortions are also considered to be treatment-related developmental effects.

Genotoxicity

Study	Species and Strain or Cell Type and Concentrations or Doses	Effects
Salmonella typhimurium and *E. Coli* in vitro bacterial gene mutation	S. typhimurium strains TA97, TA98, TA100, TA1535 and E.coli strain WP2uvr 0, 10, 15, 100, 500, 1000, or 5000 μg/plate (+S9 or -S9) Solvent: DMSO	**Negative**
Mammalian chromosomal aberration (in vitro) Mammalian cytogenetics	Human Lymphocytes 0, 5, 10, 15, 20, 25, or 30 μg/mL (+S9/-S9) Solvent: DMSO	**Positive** Weak clastogenic effect in the absence of S9 activation; however, the biological relevanceis unclear since the effect was limited to the nonactivated phase of testing and thepredominant types of aberrations (chromatid breaks and acentric fragments) are generally unstable and often associated with cytotoxicity.

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
24-month, rat (diet)	Rat—Crl:CD (BR) 92/sex/group 0, 10, 40, 200, or 400 ppm (0/0, 0.4/0.5, 1.6/2.2, 8.4/10.7, or 16.8/23.0 mg/kg bw/day, M/F)	NOAEL = 200/40 ppm (8.4/2.2, M/F) LOAEL = 400/200 ppm (M/F) (16.8/10.7 mg/kg bw/day, M/F) **No carcinogenicity**	200 ppm, F: lower bwg and food efficiency, slight hemolytic anemia (lower erythrocytes, hemoglobin, hematocrit, mean corpuscular volume) 400 ppm, M: slight hemolytic anemia (lower RBC, greater reticulocyte, mean corpuscular volume and mean corpuscular hemoglobin) with compensatory erythropoiesis and microscopic changes in the liver (focal cystic degeneration, focal hepatocellular degeneration and eosinopholic foci of cellular alterations, apoptosis) F-liver discolouration, increased Kupffer cell pigmentation (hemosiderin) and centrilobular hypertrophy at 1-year sacrifice and apoptosis, focal hepatocellular degeneration and centrilobular hypertrophy at 2-year sacrifice
Reproduction and Developmental Toxicity			
2-generation, rat (1litter/generation)	Rat— Crl:CD(BR) 30/sex/group 0, 20, 200, or 800 ppm (0/0, 1.1/1.5, 11.3/14.2, or 44.7/53.3 mg/kg bw/day, M/F)	**Maternal** NOAEL = 200 ppm (11.3/14.2 mg/kg bw/day, M/F) LOAEL = 800 ppm (44.7/53.3 mg/kg bw/day, M/F) **Offspring** NOAEL = 200 ppm (11.3/14.2 mg/kg bw/day, M/F) LOAEL = 800 ppm (44.7/53.3 mg/kg bw/day, M/F) **Reproductive** NOAEL = 800 ppm (44.7/53.3 mg/kg bw/day, M/F) LOAEL not observed	800 ppm: decreased bw/bwg and food consumption (M&F), hepatotoxicity (increased liver weights, higher alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, bilirubin, cholesterol, deacreased triglycerides, liver foci, discolouration, focal fatty changes, eosiniphilic focus and cellular alteration) 800 ppm: lower pup bw (both F_1 and F_2).

Study	Species/Strain and Doses	NOEL/NOAEL and LOEL mg/kg bw/day	Target Organ/Significant Effects/Comments
Developmental, rat	Rat—Crl:CD(BR) 25/group 0, 125, 250, 500, or 1000 mg/kg bw/day	**Maternal** NOAEL = 250 mg/kg bw/day LOAEL = 500 mg/kg bw/day **Developmental** NOAEL = 1000 mg/kg bw/day (limit dose) LOAEL not estimated **No teratogenic potential**	≥500 mg/kg bw: transient decrease in bw/bwg and food consumption
Developmental, rabbits	Hra:NZW SPF rabbits 20/group 0, 100, 350, or 1000 mg/kg bw/day	**Maternal** NOAEL = 350 mg/kg bw/day LOAEL = 1000 mg/kg bw/day **Developmental** NOAEL = 350 mg/kg bw/day LOAEL = 1000 mg/kg bw/day No teratogenic potential	1000 mg/kg bw: more abortion, decreased bw/bwg and food consumption, higher number of does with abnormal or little or no stool 1000 mg/kg bw: more abortion Since it cannot be determined whether the abortions (4 of 17) are due to maternal toxicity or developmental toxicity (or both), these abortions are also considered to be treatment-related developmental effects.

Genotoxicity

Study	Species and Strain or Cell Type and Concentrations or Doses	Effects
Salmonella typhimurium and *E. Coli* in vitro bacterial gene mutation	S. typhimurium strains TA97, TA98, TA100, TA1535 and E.coli strain WP2uvr 0, 10, 15, 100, 500, 1000, or 5000 μg/plate (+S9 or -S9) Solvent: DMSO	**Negative**
Mammalian chromosomal aberration (in vitro) Mammalian cytogenetics	Human Lymphocytes 0, 5, 10, 15, 20, 25, or 30 μg/mL (+S9/-S9) Solvent: DMSO	**Positive** Weak clastogenic effect in the absence of S9 activation; however, the biological relevanceis unclear since the effect was limited to the nonactivated phase of testing and thepredominant types of aberrations (chromatid breaks and acentric fragments) are generally unstable and often associated with cytotoxicity.

Study	Species and Strain or Cell Type and Concentrations or Doses	Effects
Mammalian chromosomal aberration (in vitro) Mammalian cytogenetics	Human Lymphocytes 0, 1, 5, 8, 10, 15, or 18 µg/mL (+S9/-S9) Solvent: DMSO	**Positive** Weak clastogenic effect in the absence of S9 activation; however, the biological relevanceis unclear since the effect was limited to the nonactivated phase of testing and the predominant types of aberrations (chromatid breaks and acentric fragments) are generally unstable and often associated with cytotoxicity. Nevertheless, the findings were reproducible and confirmed the findings from the previous study.
Mammalian chromosomal aberration (in vitro) gene forward mutation assay at the HGPRT Locus	Chinese hamster ovary cells (CHO) 100, 150, 175, 200, 250, 300, 400, 450, 500, or 600 µg/mL (+S9) 75, 100, 150, 175, 200, 250, 300, 350, 400, or 540 µg/mL (-S9) Solvent: DMSO	Negative
Mammalian chromosomal aberration (in vitro) gene forward mutation assay at the HGPRT Locus	Chinese hamster ovary cells (CHO) 5, 10, 20, or 30 µg/mL (+S9/-S9) Solvent: DMSO	**Negative**
Micronucleus Assay (in vivo) (Chromosomal aberrations)	Mouse bone marrow 0, 1250, 2500, or 5000 mg/kg bw in corn oil (limit dose)	**Negative**
UDS in vivo/in vitro	Primary rat hepatocyte 800 or 2000 mg/kg bw in corn oil (limit dose)	**Negative**
UDS in vitro	Primary rat hepatocyte 0, 0.1, 0.25, 1.5, 1.0, 2.5, or 5.0 µg/mL (19 hours) Solvent:DMSO	**Negative**
UDS in vitro	Primary rat hepatocyte 0, 0.05, 0.1, 0.25, 0.5, 1.5, 2.5, 5.0, or 7.5 µg/mL (18 hours) Solvent:DMSO	**Negative**

Study	Species and Strain or Cell Type and Concentrations or Doses		Effects
UDS in vitro	Primary rat hepatocyte 0, 0.05, 0.1, 0.5, 1.0, 5.0, 7.5, or 10 µg/mL (19 hours) Solvent:DMSO		**Negative**
SPECIAL STUDIES			
Acute Neurotoxicity (gavage)	Rats—Crl:CD(BR) (12/sex/group) 0, 500, 1000, 2000 mg/kg bw	Systemic toxicty NOAEL = 1000 mg/kg bw LOAEL = 2000 mg/kg bw **Neurotoxicity** NOAEL = 1000 mg/kg bw/day LOAEL = 2000 mg/kg bw	2000 mg/kg bw: decreased bw/bwg and food consumption (M) 2000 mg/kg bw: greater incidence of palpebral closure in males on day 1
13-week Subchronic Neurotoxicity (diet)	Rats—Crl:CD(BR) 12/sex/dose 0, 50, 200, or 800 ppm (0/0, 2.9/3.7, 11.7/14.4, or 46.9/59.3 mg/kg bw/day, M/F).	**Systemic toxicity** NOAEL= 200 ppm (11.7/14.4 mg/kg bw/day, M/F) LOAEL = 800 ppm (46.9/59.3 mg/kg bw/day, M/F) **No Evidence of Neurotoxicity**	800 ppm: decreased bw/bwg, food consumption and food efficiency
28-day Imunotoxicity, rats (diet)	Rats—Crl:CD(BR) 10/sex/group 0, 50, 100, 200, or 800 ppm (0/0, 4/4, 7/8, 14/16, or 55/57 mg/kg bw/day, M/F).	Immunotoxicity NOAEL = 800 ppm (55/57 mg/kg bw/day, M/F) LOAEL not observed Systemic Toxicity NOAEL = 200 ppm (14/16 mg/kg bw/day, M/F) LOAEL = 800 ppm (55/57 mg/kg bw/day, M/F)	There was no treatment-related effect on any of the immune parameters examined. 800 ppm : decreased bw, food consumption, food efficiency, increased spleen weight

Study	Species and Strain or Cell Type and Concentrations or Doses	Effects
Mammalian chromosomal aberration (in vitro) Mammalian cytogenetics	Human Lymphocytes 0, 1, 5, 8, 10, 15, or 18 μg/mL (+S9/-S9) Solvent: DMSO	**Positive** Weak clastogenic effect in the absence of S9 activation; however, the biological relevanceis unclear since the effect was limited to the nonactivated phase of testing and the predominant types of aberrations (chromatid breaks and acentric fragments) are generally unstable and often associated with cytotoxicity. Nevertheless, the findings were reproducible and confirmed the findings from the previous study.
Mammalian chromosomal aberration (in vitro) gene forward mutation assay at the HGPRT Locus	Chinese hamster ovary cells (CHO) 100, 150, 175, 200, 250, 300, 400, 450, 500, or 600 μg/mL (+S9) 75, 100, 150, 175, 200, 250, 300, 350, 400, or 540 μg/mL (-S9) Solvent: DMSO	Negative
Mammalian chromosomal aberration (in vitro) gene forward mutation assay at the HGPRT Locus	Chinese hamster ovary cells (CHO) 5, 10, 20, or 30 μg/mL (+S9/-S9) Solvent: DMSO	**Negative**
Micronucleus Assay (in vivo) (Chromosomal aberrations)	Mouse bone marrow 0, 1250, 2500, or 5000 mg/kg bw in corn oil (limit dose)	**Negative**
UDS in vivo/in vitro	Primary rat hepatocyte 800 or 2000 mg/kg bw in corn oil (limit dose)	**Negative**
UDS in vitro	Primary rat hepatocyte 0, 0.1, 0.25, 1.5, 1.0, 2.5, or 5.0 μg/mL (19 hours) Solvent:DMSO	**Negative**
UDS in vitro	Primary rat hepatocyte 0, 0.05, 0.1, 0.25, 0.5, 1.5, 2.5, 5.0, or 7.5 μg/mL (18 hours) Solvent:DMSO	**Negative**

Study	Species and Strain or Cell Type and Concentrations or Doses		Effects
UDS in vitro	Primary rat hepatocyte 0, 0.05, 0.1, 0.5, 1.0, 5.0, 7.5, or 10 μg/mL (19 hours) Solvent:DMSO		**Negative**
SPECIAL STUDIES			
Acute Neurotoxicity (gavage)	Rats—Crl:CD(BR) (12/sex/group) 0, 500, 1000, 2000 mg/kg bw	Systemic toxicty NOAEL = 1000 mg/kg bw LOAEL = 2000 mg/kg bw **Neurotoxicity** NOAEL = 1000 mg/kg bw/day LOAEL = 2000 mg/kg bw	2000 mg/kg bw: decreased bw/bwg and food consumption (M) 2000 mg/kg bw: greater incidence of palpebral closure in males on day 1
13-week Subchronic Neurotoxicity (diet)	Rats—Crl:CD(BR) 12/sex/dose 0, 50, 200, or 800 ppm (0/0, 2.9/3.7, 11.7/14.4, or 46.9/59.3 mg/kg bw/day, M/F).	**Systemic toxicity** NOAEL= 200 ppm (11.7/14.4 mg/kg bw/day, M/F) LOAEL = 800 ppm (46.9/59.3 mg/kg bw/day, M/F) **No Evidence of Neurotoxicity**	800 ppm: decreased bw/bwg, food consumption and food efficiency
28-day Imunotoxicity, rats (diet)	Rats—Crl:CD(BR) 10/sex/group 0, 50, 100, 200, or 800 ppm (0/0, 4/4, 7/8, 14/16, or 55/57 mg/kg bw/day, M/F)	Immunotoxicity NOAEL = 800 ppm (55/57 mg/kg bw/day, M/F) LOAEL not observed Systemic Toxicity NOAEL = 200 ppm (14/16 mg/kg bw/day, M/F) LOAEL = 800 ppm (55/57 mg/kg bw/day, M/F)	There was no treatment-related effect on any of the immune parameters examined. 800 ppm : decreased bw, food consumption, food efficiency, increased spleen weight

Study	Species and Strain or Cell Type and Concentrations or Doses		Effects
28-day Immunotoxicity—mice (diet)	Mice—Crl:CD-1 (ICR) BR 10/sex/group 0, 50, 350, 2000, or 7000 ppm (0/0, 8/11, 55/72, 327/417, or 1186/1664 mg/kg bw/day, M/F)	**Immunotoxicity** NOAEL = 7000 ppm (1186/1664 mg/kg bw/day, (M/F) LOAEL was not established	There was no treatment-related effect on any of the immune parameters examined.
		Systemic toxicity NOAEL = 7000/200 (1186/417 mg/kg bw/day, M/F) LOAEL = 7000 ppm (1664 mg/kg bw/day, F, not established for M)	7000 ppm, F: increased spleen weights
Compound-Induced Mortality:	No treatment-related mortality in short-term or chronic toxicity studies		
Recommended ARfD:	Not recommended		
Recommended ADI: **MOE for other critical endpoint(s):**	0.0014 mg/kg bw/day 7142-fold for the neurological endpoint and 25 000-fold for the developmental endpoint		

Appendix II Residue

Table 1 Integrated Food Residue Chemistry Summary Table

<table>
<tr><th colspan="7">Directions for Use of Famoxadone on Potatoes and Tomatoes</th></tr>
<tr><th>Crop</th><th>Formulation/ type</th><th>Interval (days)</th><th>Rate g a.i./ha</th><th># per season</th><th>Maximum Rate</th><th>PHI (days)</th></tr>
<tr><td>Potatoes
Tomatoes</td><td>Tanos 50DF; WDG</td><td>7</td><td>210</td><td>6</td><td>1260 g a.i./ha</td><td>14 (potato)
3 (tomato)</td></tr>
<tr><td colspan="3">Label Restrictions</td><td colspan="4">Applications may be made using ground equipment only in Canada.
Restrict rotation to crops listed on the famoxadone label and to small grains following a minimum plantback interval of 30 days and 1 year for all other rotated crops.</td></tr>
<tr><th colspan="7">Analytical Methodology</th></tr>
<tr><th>Parameters</th><th colspan="3">Plant matrices</th><th colspan="3">Animal matrices</th></tr>
<tr><td>Method ID</td><td colspan="3">AMR 3705-95 (GC-NPD); DuPont-1651 (HPLC-UV)</td><td colspan="3">DuPont-1452 (HPLC-UV); AMR 3750-96 (GC-NPD)</td></tr>
<tr><td>Type</td><td colspan="3">Data gathering and enforcement</td><td colspan="3">Data gathering and enforcement</td></tr>
<tr><td>Analyte</td><td colspan="3">Famoxadone</td><td colspan="3">Famoxadone</td></tr>
<tr><td>Instrument</td><td colspan="3">GC-NPD or column-switching HPLC-UV (tomato paste)</td><td colspan="3">GC-NPD or column-switching HPLC-UV</td></tr>
<tr><td>LOQ</td><td colspan="3">0.02 ppm (grapes, tomatoes, barley and wheat grain)
0.05 ppm (barley and wheat straw, green forage)</td><td colspan="3">HPLC-UV: LOQ 0.01 ppm (milk, kidney, muscle, fat, cream) and 0.05 ppm (liver)
GC-NPD: LOQ 0.02 ppm for all tissues, eggs and milk, except for cream (0.1 ppm)</td></tr>
<tr><td>Standard</td><td colspan="3">External bracketing standards.</td><td colspan="3">External bracketing standards</td></tr>
<tr><td>ILV</td><td colspan="3">Adequate independent laboratory validation. Several analytical methods were developed to quantitate residues of famoxadone in plant matrices. Modifications were incorporated (extraction solvent, clean-up steps) in order to minimize the fats, oils, polar and non-polar co-extracted interferences, depending on the matrices. These variations are not expected to affect the extraction profile and efficiency.</td><td colspan="3">Neither method has undergone an ILV. However, it was determined that method DuPont-1452 was similar enough to method AMR 3705-95 (plant matrix method), that the ILV can be translated to DuPont-1452. It is recommended that method DuPont-1452 be the enforcement method since it has undergone radiovalidation.</td></tr>
</table>

Study	Species and Strain or Cell Type and Concentrations or Doses		Effects
28-day Immunotoxicity—mice (diet)	Mice—Crl:CD-1 (ICR) BR 10/sex/group 0, 50, 350, 2000, or 7000 ppm (0/0, 8/11, 55/72, 327/417, or 1186/1664 mg/kg bw/day, M/F)	**Immunotoxicity** NOAEL = 7000 ppm (1186/1664 mg/kg bw/day, (M/F) LOAEL was not established	There was no treatment-related effect on any of the immune parameters examined.
		Systemic toxicity NOAEL = 7000/200 (1186/417 mg/kg bw/day, M/F) LOAEL = 7000 ppm (1664 mg/kg bw/day, F, not established for M)	7000 ppm, F: increased spleen weights
Compound-Induced Mortality:	No treatment-related mortality in short-term or chronic toxicity studies		
Recommended ARfD:	Not recommended		
Recommended ADI: **MOE for other critical endpoint(s):**	0.0014 mg/kg bw/day 7142-fold for the neurological endpoint and 25 000-fold for the developmental endpoint		

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<tr><td>Method ID</td><td colspan="3">AMR 3705-95 (GC-NPD); DuPont-1651 (HPLC-UV)</td><td colspan="3">DuPont-1452 (HPLC-UV); AMR 3750-96 (GC-NPD)</td></tr>
<tr><td>Type</td><td colspan="3">Data gathering and enforcement</td><td colspan="3">Data gathering and enforcement</td></tr>
<tr><td>Analyte</td><td colspan="3">Famoxadone</td><td colspan="3">Famoxadone</td></tr>
<tr><td>Instrument</td><td colspan="3">GC-NPD or column-switching HPLC-UV (tomato paste)</td><td colspan="3">GC-NPD or column-switching HPLC-UV</td></tr>
<tr><td>LOQ</td><td colspan="3">0.02 ppm (grapes, tomatoes, barley and wheat grain)
0.05 ppm (barley and wheat straw, green forage)</td><td colspan="3">HPLC-UV: LOQ 0.01 ppm (milk, kidney, muscle, fat, cream) and 0.05 ppm (liver)
GC-NPD: LOQ 0.02 ppm for all tissues, eggs and milk, except for cream (0.1 ppm)</td></tr>
<tr><td>Standard</td><td colspan="3">External bracketing standards.</td><td colspan="3">External bracketing standards</td></tr>
<tr><td>ILV</td><td colspan="3">Adequate independent laboratory validation. Several analytical methods were developed to quantitate residues of famoxadone in plant matrices. Modifications were incorporated (extraction solvent, clean-up steps) in order to minimize the fats, oils, polar and non-polar co-extracted interferences, depending on the matrices. These variations are not expected to affect the extraction profile and efficiency.</td><td colspan="3">Neither method has undergone an ILV. However, it was determined that method DuPont-1452 was similar enough to method AMR 3705-95 (plant matrix method), that the ILV can be translated to DuPont-1452. It is recommended that method DuPont-1452 be the enforcement method since it has undergone radiovalidation.</td></tr>
</table>

Analytical Methodology		
Parameters	**Plant matrices**	**Animal matrices**
Extraction	Extraction of sample matrices with aqueous acetonitrile, clean-up by solvent partitioning into hexane followed by passage through a Florisil column or various solid-phase extraction (SPE) cartridges.	HPLC-UV: Milk and tissue samples are extracted by MSPD, using octadecylsilyl-derivatized packing as a support and acetonitrile as eluent. Sample clean-up using disposable alumina, carbon and silica solid phase extraction cartridges GC-NPD: Extraction of sample matrices with aqueous acetonitrile, salting-out of the aqueous acetonitrile sample extract and clean-up by hexane solvent partitioning and Florisil column
Radiovalidation	The method was adequately radiovalidated using bioincurred residues from plant metabolism studies.	Only method DuPont-1452 was radiovalidated using samples from the goat metabolism study.
Multiresidue method	Famoxadone was screened through multiresidue methods listed in the Pesticide Analytical Manual Volume I (PAM Vol. I), Third Edition (January 1994), using Protocols C to E. Good recoveries were obtained for the analysis of wine, grapes and tomatoes (92–138%) using Protocol D and grapes (red seedless) using Protocol E (92–108%).	
Nature of the Residue in Plants		
Parameters	**Plant matrices**	**Animal matrices**
Method ID	AMR 3705-95 (GC-NPD); DuPont-1651 (HPLC-UV)	DuPont-1452 (HPLC-UV); AMR 3750-96 (GC-NPD)
Type	Data gathering and enforcement	Data gathering and enforcement
Analyte	Famoxadone	Famoxadone
Instrument	GC-NPD or column-switching HPLC-UV (tomato paste)	GC-NPD or column-switching HPLC-UV
LOQ	0.02 ppm (grapes, tomatoes, barley and wheat grain) 0.05 ppm (barley and wheat straw, green forage)	HPLC-UV: LOQ 0.01 ppm (milk, kidney, muscle, fat, cream) and 0.05 ppm (liver). GC-NPD: LOQ 0.02 ppm for all tissues, eggs and milk, except for cream (0.1 ppm).
Standard	External bracketing standards	External bracketing standards

Nature of the Residue in Plants

Parameters	Plant matrices	Animal matrices
Independent Laboratory Validation	Adequate independent laboratory validation. Several analytical methods were developed to quantitate residues of famoxadone in plant matrices. Modifications were incorporated (extraction solvent, clean-up steps) in order to minimize the fats, oils, polar and non-polar co-extracted interferences, depending on the matrices. These variations are not expected to affect the extraction profile and efficiency.	Neither method has undergone an ILV. However, it was determined that method DuPont-1452 was similar enough to method AMR 3705-95 (plant matrix method), that the ILV can be translated to DuPont-1452. It is recommended that method DuPont-1452 be the enforcement method since it has undergone radiovalidation.
Extraction	Extraction of sample matrices with aqueous acetonitrile, clean-up by solvent partitioning into hexane followed by passage through a Florisil column or various solid-phase extraction (SPE) cartridges.	HPLC-UV: Milk and tissue samples are extracted by MSPD, using octadecylsilyl-derivatized packing as a support and acetonitrile as eluent. Sample clean-up using disposable alumina, carbon and silica solid phase extraction cartridges GC-NPD: Extraction of sample matrices with aqueous acetonitrile, salting-out of the aqueous acetonitrile sample extract and clean-up by hexane solvent partitioning and Florisil column.
Radiovalidation	The method was adequately radiovalidated using bioincurred residues from plant metabolism studies.	Only method DuPont-1452 was radiovalidated using samples from the goat metabolism study.
Multiresidue method	Famoxadone was screened through multiresidue methods listed in the Pesticide Analytical Manual Volume I (PAM Vol. I), Third Edition (January 1994), using Protocols C to E. Good recoveries were obtained for the analysis of wine, grapes and tomatoes (92–138%) using Protocol D and grapes (red seedless) using Protocol E (92–108%).	

Nature of the Residue in Plants

Species	Radiolabel	Dose Level	Sacrifice
Goat (Alpine and Toggenburg)	(^{14}C-Phenoxyphenyl or ^{14}C-Phenylamino) DPX-JE874 (58–62 μCi/mg)	10 mg/kg bw/day for seven consecutive days	23 hrs after first administration
Radioactive residues in the feces accounted for over 82–89% of the administered dose. The total ^{14}C-residues in the urine accounted for 1.2% of the administered dose (POP-label) and 4.6% of the administered dose (PA-label). The sum of the total ^{14}C-residues in the liver, kidney, muscle, fat, blood, bile and milk accounted for less than 0.5% of the administered dose. Most of the remaining radiolabel was presumed to be present in the gastrointestinal tract of these animals upon termination.			

Analytical Methodology

Parameters	Plant matrices	Animal matrices
Extraction	Extraction of sample matrices with aqueous acetonitrile, clean-up by solvent partitioning into hexane followed by passage through a Florisil column or various solid-phase extraction (SPE) cartridges.	HPLC-UV: Milk and tissue samples are extracted by MSPD, using octadecylsilyl-derivatized packing as a support and acetonitrile as eluent. Sample clean-up using disposable alumina, carbon and silica solid phase extraction cartridges GC-NPD: Extraction of sample matrices with aqueous acetonitrile, salting-out of the aqueous acetonitrile sample extract and clean-up by hexane solvent partitioning and Florisil column
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Type	Data gathering and enforcement	Data gathering and enforcement
Analyte	Famoxadone	Famoxadone
Instrument	GC-NPD or column-switching HPLC-UV (tomato paste)	GC-NPD or column-switching HPLC-UV
LOQ	0.02 ppm (grapes, tomatoes, barley and wheat grain) 0.05 ppm (barley and wheat straw, green forage)	HPLC-UV: LOQ 0.01 ppm (milk, kidney, muscle, fat, cream) and 0.05 ppm (liver) GC-NPD: LOQ 0.02 ppm for all tissues, eggs and milk, except for cream (0.1 ppm).
Standard	External bracketing standards	External bracketing standards

Nature of the Residue in Plants

Parameters	Plant matrices	Animal matrices
Independent Laboratory Validation	Adequate independent laboratory validation. Several analytical methods were developed to quantitate residues of famoxadone in plant matrices. Modifications were incorporated (extraction solvent, clean-up steps) in order to minimize the fats, oils, polar and non-polar co-extracted interferences, depending on the matrices. These variations are not expected to affect the extraction profile and efficiency.	Neither method has undergone an ILV. However, it was determined that method DuPont-1452 was similar enough to method AMR 3705-95 (plant matrix method), that the ILV can be translated to DuPont-1452. It is recommended that method DuPont-1452 be the enforcement method since it has undergone radiovalidation.
Extraction	Extraction of sample matrices with aqueous acetonitrile, clean-up by solvent partitioning into hexane followed by passage through a Florisil column or various solid-phase extraction (SPE) cartridges.	HPLC-UV: Milk and tissue samples are extracted by MSPD, using octadecylsilyl-derivatized packing as a support and acetonitrile as eluent. Sample clean-up using disposable alumina, carbon and silica solid phase extraction cartridges. GC-NPD: Extraction of sample matrices with aqueous acetonitrile, salting-out of the aqueous acetonitrile sample extract and clean-up by hexane solvent partitioning and Florisil column.
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Nature of the Residue in Plants

Species	Radiolabel	Dose Level	Sacrifice
Hen (British Saanen laying hens)	(^{14}C-Phenoxyphenyl or ^{14}C-Phenylamino) DPX-JE874 (55–60 µCi/mg)	10 mg/kg bw/day for seven consecutive days	22 hrs after first administration

The overall metabolic profile of ^{14}C-POP and ^{14}C-PA famoxadone was qualitatively similar and resulted in rapid elimination of famoxadone in the excreta (>90%) and low distribution and retention of ^{14}C-residues in eggs (<0.1%) and edible organs/tissues (<0.5%).

Matrices	Major metabolites (>10% TRRs)	Minor metabolites
Hen excreta	Famoxadone, IN-MP821	IN-KZ007, IN-KZ532, IN-KZ534, IN-MQ610, IN-ML815/KF015, IN-ME338, IN-H3310, IN-KZ2000, IN-MQ608, IN-MQ609, IN-JS940
Hen liver	IN-KZ007	IN-KZ534, IN-KZ532
Hen egg yolk	IN-KZ007	Famoxadone, IN-KZ532
Goat muscle	Famoxadone	—
Goat liver	Famoxadone	IN-KZ007, IN-KZ2000, IN-KZ532
Goat kidney	Famoxadone	—
Goat fat	Famoxadone	—
Goat milk	Famoxadone	—

Storage Stability

The data indicate that residues of famoxadone are stable during frozen storage in potatoes, grapes, wheat forage, straw, grain, tomatoes, peppers and soil for up to 18 months. These durations are adequate to support the crop field trials submitted to support the petitioned uses. No correction to residue values due to in-storage dissipation is necessary.

Crop Field Trials—Potatoes and Tomatoes

The number (24) and location of the field trials for potato are adequate and in representative growing regions (1, 1A, 2, 3, 5, 5A, 5B, 9, 10, 11, 14). The number of field trials (25) for tomatoes is adequate and in a variety of growing regions (1, 2, 3, 5, 10), although trials were under-represented in Canada's growing region 5/5B. However, sufficient data are available to establish a MRL on tomatoes that will cover the dietary intake of tomatoes during all seasons.

Commodity	Application Rate kg a.i./ha/season	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean	SDEV
Potato tuber	1.25 (onefold)	14	Famoxadone	32	<0.02	<0.02	<0.02	<0.02	0
Tomato (1999)	1.25 (onefold)	3	Famoxadone	22	0.1	0.48	0.43	0.23	0.13
Tomato (2001)	1.25 (onefold)	3	Famoxadone	26	0.13	0.79	0.71	0.28	0.17

Maximum Residue Limits

potatoes	0.02 ppm
tomatoes	1.0 ppm
cattle, horse, goat, sheep, liver	0.05 ppm
cattle, horse, goat, sheep, fat	0.02 ppm
milk, fat (reflecting negligible residue in whole milk)	0.06 ppm

Field Accumulation in Rotational Crops—Radish, Spinach, Wheat

DPX-KP481 50 WG Fungicide, formulated as a wettable granule (WG) containing 25% famoxadone and 25% cymoxanil by weight as active ingredients (50% total a.i.), was applied to growing tomatoes (primary crop) six times each at a rate of 210 g a.i./ha with 5-day interval, for a total seasonal application rate of 1260 g a.i./ha (onefold). Representative root (radish), leafy (spinach) and small grain crops (wheat) were planted 17, 33 and 63 DAT. Residues of famoxadone were below the LOQ of the analytical method (0.01 ppm) in radish tops (leaves), radish roots, spinach leaves and wheat forage, hay, grain and straw at normal harvest at all plantback intervals examined. However, the experimental design did not include the analysis of the potential residues of concern for rotational crops (famoxadone, IN-MQ613, IN-KZ534, IN-KZ007). Based on the data from the confined study indicating that famoxadone is the principle residue in wheat matrices at 30 days, the overall low level of residues in the confined study, and on the lack of famoxadone residues in the field rotational study, we are recommending that the label for formulations containing famoxadone be modified to restrict rotation to crops listed on the famoxadone label at any time, and to small grains following a minimum plantback interval of 30 days and 1 year for all other rotated crops.

Processed Food and Feed

The field trials that supplied the potatoes and tomatoes for the processing studies were carried out at exaggerated rates of fivefold and sixfold, respectively. Processing followed typical commercial practices and the residue data are supported by the analytical methods and storage stability studies. Based on the processing factors and the highest average field trials for the potatoes and tomatoes, residues in the processed commodity will be covered by the recommended MRL for the RAC.

Livestock Feeding

Encapsulated famoxadone was administered orally twice daily to fourteen adult Holstein acclimatized dairy cattle (Bos taurus) for 28 consecutive days at 9, 27,and 90 μg famoxadone/g feed. Of the currently requested uses, only potato is a significant livestock feed item. Using a diet containing potato culls and processing waste, the maximum theoretical dietary burden is estimated to be 0.1 ppm. The LOQ for the more sensitive livestock analytical method (DuPont-1452) is 0.010 ppm for milk, kidney, muscle, fat and cream and 0.05 ppm for liver. Based on a dietary burden of 0.1 ppm, the potential residues of famoxadone in cattle matrices are at or below their respective LOQs. However, famoxadone residues were lower in skim milk than in whole milk but transferred to cream. An MRL will be established in milk fat to take into account residues in cream.

Nature of the Residue in Plants

Species	Radiolabel	Dose Level	Sacrifice
Hen (British Saanen laying hens)	(^{14}C-Phenoxyphenyl or ^{14}C-Phenylamino) DPX-JE874 (55–60 µCi/mg)	10 mg/kg bw/day for seven consecutive days	22 hrs after first administration

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Goat fat	Famoxadone	—
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Table 2 Overview of Plant/Animals Metabolism Studies and Risk Assessment

Plant Metabolism Studies		
Crops (*n*=3)	Tomato, potato, grapes	
ROC for Monitoring and MRL	Famoxadone (primary crops); rotational crops (no decision at this time)	
ROC for Risk Assessment	Famoxadone (primary crops); famoxadone, IN-MQ613, IN-KZ534 and IN-KZ007 (rotational crops)	
Metabolic Profile in Diverse Crops	Metabolism in potatoes and tomatoes is adequately understood. Although the metabolic profiles from the studied crops are similar, the data are not sufficient to claim an understanding of the nature of the residue in all crops. To adequately understand metabolism in target plants, an additional metabolism study may be required.	
Animal Metabolism Studies		
Animals (*n*=2)	lactating goat	laying hen
ROC for Monitoring and MRL	Famoxadone	Decision deferred until the nature of the residue in poultry is adequately understood.
ROC for Risk Assessment	Famoxadone	Famoxadone, IN-KZ007, IN-KZ532, IN-KZ534
Metabolic Profile in Animals	Ruminant metabolism adequately understood. The metabolism study with laying hens is not sufficient for delineating the nature of the residue in poultry. Radioactive residues in poultry liver were not adequately identified or characterized. At this time, however, there are no requested uses that would result in residues on significant poultry feed items. For use expansion, the petitioner will be required to provide more complete data regarding residues in poultry liver for uses which would result in residues on significant poultry feed items.	
Fat-soluble Residue	Yes	

Dietary Risk from Food and Water			
Chronic Non-Cancer Dietary Risk ADI = 0.0014 mg/kg bw/day EEC = 0.25 μg/L Intermediate refinements used	**Population**	**Estimated Risk (% of ADI)**	
		Food	**Food + EEC**
	All infants < 1 yr old	12.9	14.2
	Children 1 to 2 yrs	76.9	77.5
	Children 3 to 5 yrs	68.7	69.2
	Children 6 to 12 yrs	45	45.4
	Youth 13 to 19 yrs	29.8	30
	Adults 20 to 49 yrs	32.8	33.1
	Adults 50+ yrs	32.5	32.8
	Total Population	36.4	36.8

Table 2 Overview of Plant/Animals Metabolism Studies and Risk Assessment

Plant Metabolism Studies		
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	Total Population	36.4	36.8

Appendix III Environmental Assessment

Table 1 Physical and chemical properties of the active ingredient relevant to the environment

Property	**Test substance**	**Value**	**Comments**
Water solubility at 20°C (mg/L)	Famoxadone (96%)	**pH** **μg/L ±s.d.** 5 243 ± 271 7 111 ± 89 9 38 ± 16	Sparingly soluble to insoluble in water
Vapour pressure at 20°C	Famoxadone (99.6%)	4.8×10^{-9} mm Hg (6.4×10^{-7} Pa m^3mol^{-1})	Not likely to volatilize from water and moist soil surfaces
Henry's Law Constant at 20°C	Famoxadone (99.6%)	5.387×10^5 (4.6×10^{-3} Pa m^3mol^{-1})	
log K_{ow}	Famoxadone (99.6%)	**pH** **Log K_{ow} ± sd** 5.0 4.80 ± 0.13 7.0 4.65 ± 0.40 9.0 5.55 ± 0.26	Potential for bioaccumulation
pK_a	Famoxadone (99.6%)	No value given	The dissociation constant could not be measured directly due to the low solubility in water. Based on the chemical structure, famoxadone is expected to be weakly basic.
UV–visible absorption	Famoxadone (99.6%)	λmax = 231 nm	Not likely to undergo phototransformation

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Henry's Law Constant at 20°C	Famoxadone (99.6%)	$5.387 \times 10^{[illegible]}$ (4.6×10^{-3} Pa m^{3}mol^{-1})	
log K_{ow}	Famoxadone (99.6%)	**pH** **Log K_{ow} ± sd** 5.0 4.80 ± 0.13 7.0 4.65 ± 0.40 9.0 5.55 ± 0.26	Potential for bioaccumulation
pK_a	Famoxadone (99.6%)	No value given	The dissociation constant could not be measured directly due to the low solubility in water. Based on the chemical structure, famoxadone is expected to be weakly basic.
UV-visible absorption	Famoxadone (99.6%)	λmax = 231 nm	Not likely to undergo phototransformation

Table 2 Summary of abiotic transformation processes

Process	Half-life	Major transformation products	Minor transformation products	Comments
Hydrolysis	pH 5 = 31–41 d pH 7 = 2–2.7 d pH 9 = 1.55–1.8 h	IN-JS940 (pH 5, 7, 9) IN-JL856 (pH 7, 9) IN-H3310 (pH 7) IN-MN968 (pH 9)	IN-H3310 (pH 5, 9) IN-JL856 (pH 5) polars (14–22.2%) phenols (4.5–10.9%)	This is an important route of transformation in the environment in neutral to alkaline solutions and transformation is slow in acidic solutions.
Phototransformation —water	Dark: pH 5 = 41 d Irradiated: pH 5 = 1.1–1.9 d	Dark: IN-JS940 Irradiated: IN-JS940 IN-H3310 CO$_2$ = 13.3% Organic volatiles = 3.7%	Dark: IN-H3310 IN-JL856 Irradiated: IN-JL856 IN-KF015	Phototransformation in water may be an important route of transformation
Phototransformation —soil	Dark: ≥30.8 d Irradiated: 3.4–5.8 d (corrected for the dark controls)	Dark: IN-H3310 Irradiated: IN-H3310 IN-MN467 IN-MN468 IN-KF015 CO$_2$ = 30.3%	Dark: IN-MN468 IN-MN467 Irradiated: IN-JS940	Phototransformation on soil may be an important route of transformation

Table 3 Summary of biotransformation

Process	DT_{50}	Major transformation products	Minor transformation products	Comments
Aerobic soil biotransformation	German soil: $DT_{50} = 6$ d $DT_{90} = 134$ d	None	IN-KZ007 IN-JS940 IN-MN467	Non-persistent
	Ohio soil: $DT_{50} = 9$ d $DT_{90} = 248$ d	None	IN-KZ007 IN-JS940 IN-MN467	
	UK soil: $DT_{50} = 11$ d $DT_{90} = 186$ d	IN-KZ007	IN-JS940 IN-MN467	
	Delaware soil: $DT_{50} = 3$ d $DT_{90} = 136$ d	IN-JS940	IN-KZ007 IN-MN467	
	French soil: $DT_{50} = 2$ d $DT_{90} = 56$ d	None	IN-KZ007 IN-JS940 IN-MN467	
Anaerobic soil biotransformation	German soil: $DT_{50} = 28$ d $DT_{90} = 91$ d	IN-JS940	IN-KZ007 IN-H3310	Slightly persistent
Aerobic water/sediment biotransformation	Ohio —whole system $DT_{50} = 0.68–2.05$ d $DT_{90} = 14.3–53.5$ d			Non-persistent
	—water	IN-JS940	IN-H3310 IN-JL856/ IN-KZ007	
	—sediment	IN-H3310	IN-JS940 IN-KZ007 IN-JL856	

Table 2 Summary of abiotic transformation processes

Process	Half-life	Major transformation products	Minor transformation products	Comments
Hydrolysis	pH 5 = 31–41 d pH 7 = 2–2.7 d pH 9 = 1.55–1.8 h	IN-JS940 (pH 5, 7, 9) IN-JL856 (pH 7, 9) IN-H3310 (pH 7) IN-MN968 (pH 9)	IN-H3310 (pH 5, 9) IN-JL856 (pH 5) polars (14–22.2%) phenols (4.5–10.9%)	This is an important route of transformation in the environment in neutral to alkaline solutions and transformation is slow in acidic solutions.
Phototransformation —water	Dark: pH 5 = 41 d Irradiated: pH 5 = 1.1–1.9 d	Dark: IN-JS940 Irradiated: IN-JS940 IN-H3310 CO_2 = 13.3% Organic volatiles = 3.7%	Dark: IN-H3310 IN-JL856 Irradiated: IN-JL856 IN-KF015	Phototransformation in water may be an important route of transformation
Phototransformation —soil	Dark: >30.8 d Irradiated: 3.4–5.8 d (corrected for the dark controls)	Dark: IN-H3310 Irradiated: IN-H3310 IN-MN467 IN-MN468 IN-KF015 CO_2 = 30.3%	Dark: IN-MN468 IN-MN467 Irradiated: IN-JS940	Phototransformation on soil may be an important route of transformation

Table 3 Summary of biotransformation

Process	DT_{50}	Major transformation products	Minor transformation products	Comments
Aerobic soil biotransformation	German soil: $DT_{50} = 6$ d $DT_{90} = 134$ d	None	IN-KZ007 IN-JS940 IN-MN467	Non-persistent
	Ohio soil: $DT_{50} = 9$ d $DT_{90} = 248$ d	None	IN-KZ007 IN-JS940 IN-MN467	
	UK soil: $DT_{50} = 11$ d $DT_{90} = 186$ d	IN-KZ007	IN-JS940 IN-MN467	
	Delaware soil: $DT_{50} = 3$ d $DT_{90} = 136$ d	IN-JS940	IN-KZ007 IN-MN467	
	French soil: $DT_{50} = 2$ d $DT_{90} = 56$ d	None	IN-KZ007 IN-JS940 IN-MN467	
Anaerobic soil biotransformation	German soil: $DT_{50} = 28$ d $DT_{90} = 91$ d	IN-JS940	IN-KZ007 IN-H3310	Slightly persistent
Aerobic water/sediment biotransformation	Ohio —whole system $DT_{50} = 0.68–2.05$ d $DT_{90} = 14.3–53.5$ d			Non-persistent
	—water	IN-JS940	IN-H3310 IN-JL856/ IN-KZ007	
	—sediment	IN-H3310	IN-JS940 IN-KZ007 IN-JL856	

Table 4 Fate and behaviour of famoxadone in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Famoxadone	**Half-life** pH 5 = 31–41 d pH 7 = 2–2.7 d pH 9 = 1.55–1.8 h	This is an important route of transformation in the environment at neutral to alkaline solutions, and transformation is slow in acid solutions. IN-JS940, IN-JL856, IN-H3310 and IN-MN968 were major transformation products.
Phototransformation on soil	Famoxadone	**Half-life** Dark: 30.8 d Irradiated: 3.4–5.8 d (corrected for dark controls)	Phototransformation on soil may be an important route of transformation. IN-H3310, IN-MN467, IN-MN468 and IN-KF015 were major transformation products.
Phototransformation in air	Famoxadone	Not required—not volatile	
Biotransformation			
Biotransformation in aerobic soil	Famoxadone	DT_{50}: 2–11 d DT_{90}: 56–248 d	IN-KZ007 and IN-JS940 were major transformation products in 1 of 5 soils. Biphasic transformation Non-persistent
	IN-KZ007	DT_{50}: 1.5–10.3 d DT_{90}: 4.9–34.3 d	Non-persistent
	IN-KF015	DT_{50}: 1.2 d DT_{90}: 4 d	Non-persistent
	IN-JS940	DT_{50}: 6–23 h DT_{90}: 18–77 h	Non-persistent
Biotransformation in anaerobic soil	Famoxadone	DT_{50}: 28 d DT_{90}: 91 d	IN-JS940 was the major transformation product. Slightly persistent

Property	Test substance	Value	Comments
Mobility			
Adsorption/desorption in soil	Famoxadone	Adsorption K_{oc}: 3300–4030	Slightly mobile
	IN-KZ007	Adsorption K_{oc}: 1238–>5000	Low mobility to immobile
	IN-KF015	Adsorption K_{oc}: 130–1300	Low to high mobility
	IN-JS940	Adsorption K_{oc}: 33–591	Low to very high mobility
Volatilization	Famoxadone	not volatile	
Field studies			
Field dissipation—Ecoregions 5.3, 8.1, 9.2 and 10.1	DPX-KP481 50 DF (Tanos 50 DF)	DT_{50}: 5–26 d DT_{90}: 17–92 d	Non-persistent to slightly persistent The parent compound was detected primarily in the top 0–15 cm soil layer.

Table 5 Fate and behaviour of famoxadone in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	Famoxadone	**Half-life** pH 5 = 31–41 d pH 7 = 2–2.7 d pH 9 = 1.55–1.8 h	An important route of transformation in the environment in neutral to alkaline solutions and transformation is slow in acidic solutions.
Phototransformation in water	Famoxadone	**Half-life** Dark: 41 d Irradiated: 1.1–1.9 d	Phototransformation in water may be an important route of transformation. IN-JS940 and IN-H3310 were major transformation products.
Biotransformation			
Biotransformation in aerobic water/sediment systems	Famoxadone	Whole system: DT_{50} = 0.68–2.05 d DT_{90} = 14.3–53.5 d	Non-persistent IN-JS940 was the major transformation product in aerobic water. IN-H3310 was the major transformation product in aerobic sediment.

Table 4 Fate and behaviour of famoxadone in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Famoxadone	**Half-life** pH 5 = 31–41 d pH 7 = 2–2.7 d pH 9 = 1.55–1.8 h	This is an important route of transformation in the environment at neutral to alkaline solutions, and transformation is slow in acid solutions. IN-JS940, IN-JL856, IN-H3310 and IN-MN968 were major transformation products.
Phototransformation on soil	Famoxadone	**Half-life** Dark: 30.8 d Irradiated: 3.4–5.8 d (corrected for dark controls)	Phototransformation on soil may be an important route of transformation. IN-H3310, IN-MN467, IN-MN468 and IN-KF015 were major transformation products.
Phototransformation in air	Famoxadone	Not required—not volatile	
Biotransformation			
Biotransformation in aerobic soil	Famoxadone	DT_{50}: 2–11 d DT_{90}: 56–248 d	IN-KZ007 and IN-JS940 were major transformation products in 1 of 5 soils. Biphasic transformation Non-persistent
	IN-KZ007	DT_{50}: 1.5–10.3 d DT_{90}: 4.9–34.3 d	Non-persistent
	IN-KF015	DT_{50}: 1.2 d DT_{90}: 4 d	Non-persistent
	IN-JS940	DT_{50}: 6-23 h DT_{90}: 18–77 h	Non-persistent
Biotransformation in anaerobic soil	Famoxadone	DT_{50}: 28 d DT_{90}: 91 d	IN-JS940 was the major transformation product. Slightly persistent

Property	Test substance	Value	Comments
Mobility			
Adsorption/desorption in soil	Famoxadone	Adsorption K_{oc}: 3300–4030	Slightly mobile
	IN-KZ007	Adsorption K_{oc}: 1238–>5000	Low mobility to immobile
	IN-KF015	Adsorption K_{oc}: 130–1300	Low to high mobility
	IN-JS940	Adsorption K_{oc}: 33–591	Low to very high mobility
Volatilization	Famoxadone	not volatile	
Field studies			
Field dissipation—Ecoregions 5.3, 8.1, 9.2 and 10.1	DPX-KP481 50 DF (Tanos 50 DF)	DT_{50}: 5–26 d DT_{90}: 17–92 d	Non-persistent to slightly persistent The parent compound was detected primarily in the top 0–15 cm soil layer.

Table 5 Fate and behaviour of famoxadone in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	Famoxadone	**Half-life** pH 5 = 31–41 d pH 7 = 2–2.7 d pH 9 = 1.55–1.8 h	An important route of transformation in the environment in neutral to alkaline solutions and transformation is slow in acidic solutions.
Phototransformation in water	Famoxadone	**Half-life** Dark: 41 d Irradiated: 1.1–1.9 d	Phototransformation in water may be an important route of transformation. IN-JS940 and IN-H3310 were major transformation products.
Biotransformation			
Biotransformation in aerobic water/sediment systems	Famoxadone	Whole system: DT_{50} = 0.68–2.05 d DT_{90} = 14.3–53.5 d	Non-persistent IN-JS940 was the major transformation product in aerobic water. IN-H3310 was the major transformation product in aerobic sediment.

Table 6 Maximum EEC in vegetation and insects after a direct over-spray of famoxadone at the maximum annual application rate (1.26 kg a.i./ha)

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	270	3.3[b]	890
Leaves and leafy crops	141	11[b]	1552
Long grass	124	4.4[b]	543
Forage crops	151	5.4[b]	817
Small insects	66	3.8[c]	249
Pods with seeds	14	3.9[c]	53
Large insects	11	3.8[c]	43
Grain and seeds	11	3.8[c]	43
Fruit	17	7.6[c]	128

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994)

[b, c] Fresh/dry weight ratios from [b]Harris (1975) and [c]Spector (1956)

Table 7 Maximum EEC of famoxadone in diets of birds and mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	220.6
Mallard duck	30% large insects 70% grain	42.6
Rat	70% short grass 20% grain/seeds 10% large insects	635.7
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	631.8
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	950.5

Table 8 Effects of famoxadone on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute	Famoxadone (97.4%)	LC_{50} = 470 mg a.i./kg soil EC_{50} > 1000 mg a.i./kg soil NOEC = 62.5 mg a.i./kg soil (M) LOEC = 125 mg a.i./kg soil	---
Bee	Oral	Famoxadone (97.7%)	LC_{50} > 400 μg a.i./bee NOEC = 400 μg a.i./bee (M)	practically non-toxic[c]
	Contact	Famoxadone (97.7%)	LC_{50} > 25 μg a.i./bee NOEC = 25 μg a.i./bee (M)	practically non-toxic[c]
Predatory mite (Typhlordomus pyri) —supplemental	Contact	DPX-KX007 SC 1.1× DPX-KX007 WG 1.1× DPX-KX007 WG 2.2×	25.3% (M), 44–100% (B) 34.7% (M), 100% (B) 42.4% (M), 100% (B)	Slightly harmful to harmful[b]
Foliage-dwelling predators green lacewing (Chrysoperia carnea)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	0–23% (M) 4.1% (F)	Harmless[b]
Foliage-dwelling predators hoverfly (Ephisyrphus balteatus)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	0–6% (M) 28–49% (F) 50–69% (E)	Harmless to slightly harmful[b]
Soil dwellers ground beetle (Poecilus cupreus L.)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	0% (M)	Harmless[b]
Soil dwellers Staphylinid beetle (Aleochara bilineata Gyll.)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	9.4% (M) 2.65 (F)	Harmless[b]

Table 6 Maximum EEC in vegetation and insects after a direct over-spray of famoxadone at the maximum annual application rate (1.26 kg a.i./ha)

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	270	3.3[b]	890
Leaves and leafy crops	141	11[b]	1552
Long grass	124	4.4[b]	543
Forage crops	151	5.4[b]	817
Small insects	66	3.8[c]	249
Pods with seeds	14	3.9[c]	53
Large insects	11	3.8[c]	43
Grain and seeds	11	3.8[c]	43
Fruit	17	7.6[c]	128

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994)

[b, c] Fresh/dry weight ratios from [b]Harris (1975) and [c]Spector (1956)

Table 7 Maximum EEC of famoxadone in diets of birds and mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	220.6
Mallard duck	30% large insects 70% grain	42.6
Rat	70% short grass 20% grain/seeds 10% large insects	635.7
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	631.8
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	950.5

Table 8 Effects of famoxadone on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute	Famoxadone (97.4%)	LC_{50} = 470 mg a.i./kg soil EC_{50} > 1000 mg a.i./kg soil NOEC = 62.5 mg a.i./kg soil (M) LOEC = 125 mg a.i./kg soil	
Bee	Oral	Famoxadone (97.7%)	LC_{50} > 400 µg a.i./bee NOEC = 400 µg a.i./bee (M)	practically non-toxic[c]
	Contact	Famoxadone (97.7%)	LC_{50} > 25 µg a.i./bee NOEC = 25 µg a.i./bee (M)	practically non-toxic[c]
Predatory mite (Typhlordomus pyri) —supplemental	Contact	DPX-KX007 SC 1.1× DPX-KX007 WG 1.1× DPX-KX007 WG 2.2×	25.3% (M), 44–100% (B) 34.7% (M), 100% (B) 42.4% (M), 100% (B)	Slightly harmful to harmful[b]
Foliage-dwelling predators green lacewing (Chrysoperia carnea)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	0–23% (M) 4.1% (F)	Harmless[b]
Foliage-dwelling predators hoverfly (Ephisyrphus balteatus)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	0–6% (M) 28–49% (F) 50–69% (E)	Harmless to slightly harmful[b]
Soil dwellers ground beetle (Poecilus cupreus L.)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	0% (M)	Harmless[b]
Soil dwellers Staphylinid beetle (Aleochara bilineata Gyll.)	Contact	DPX-KP481 WG (25% famoxadone, 25% cymoxanil) 0.7 kg formulation/ha	9.4% (M) 2.65 (F)	Harmless[b]

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Birds				
Bobwhite quail	Acute Oral	Famoxadone (97.4%)	LD_{50} > 2250 mg a.i./kg bw NOEL = 2250 mg a.i./kg bw (M)	Practically non-toxic
		DPX-KX007-5 WG (22.7% famoxadone, 30.4% cymoxanil) 2250 mg formulation/kg	LD_{50} > 2250 mg/kg bw NOEL = 292 mg/kg bw (W)	Practically non-toxic
	Dietary	Famoxadone (97.4%)	LC_{50} > 5620 mg a.i./kg diet NOEL = 5620 mg a.i./kg diet (M)	Practically non-toxic
	Reproduction	Famoxadone (97.4%)	NOEC = 46 mg a.i./kg diet (M, R) LOEC = 252 mg a.i./kg diet	—
Mallard duck	Dietary	Famoxadone (97.4%)	LC_{50} > 5620 mg a.i./kg diet NOEL = 5620 mg a.i./kg diet (M)	Practically non-toxic
	Reproduction	Famoxadone (97.4%)	NOEC = 46 mg a.i./kg diet (M,R) LOEC = 252 mg a.i./kg diet	—
Mammals				
Rat	Acute	Famoxadone	LD_{50} = 3100 mg/kg bw	Low
		Tanos 50DF	LD_{50} = 1311 mg EP/kg bw	Moderate
	Dietary	Famoxadone	NOAEL: 3.34 mg/kg bw/d (male) 4.24 mg/kg bw/d (female)	—
	Dermal	Tanos 50DF	LD_{50} > 5000 mg EP/kg bw	Low
	Inhalation	Famoxadone	LC_{50} > 5.3 mg/L	Low
		Tanos 50DF	LC_{50} > 5.1 mg EP/L	Low
	Oncogenicity	Famoxadone	NOAEL: 8.4 mg/kg bw/d (male) 2.2 mg/kg bw/d (female)	—
	2-Generation Reproduction	Famoxadone	NOAEL: 11.3 mg/kg bw/d (male) 14.2 mg/kg bw/d (female)	—
	Development	Famoxadone	NOAEL: 250 mg/kg bw/d	—

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Mouse	Dietary	Famoxadone	NOAEL: 62.4 mg/kg bw/d (male) 79.9 mg/kg bw/d (female)	—
	Oncogenicity	Famoxadone	NOAEL: 96 mg/kg bw/d (male) 130 mg/kg bw/d (female)	—
Rabbit	Dermal	Famoxadone	LD$_{50}$ > 2000 mg/kg	Low
	Development	Famoxadone	NOAEL: 350 mg/kg bw/d	—
Dog	Dietary	Famoxadone	NOAEL: 1.3 mg/kg bw/d (male) NA (female)	—
Monkey	Oncogenicity	Famoxadone	NOAEL: 100 mg/kg bw/d	—
Vascular plants				
Vascular plant	Seedling emergence	DPX-JE874 10EC (9.2% famoxadone) 2.28 kg formulation/ha	EC$_{25}$ > 2.28 kg/ha NOEC = 2.28 kg/ha	—
	Vegetative vigour	DPX-JE874 10EC (9.2% famoxadone) 2.28 kg formulation/ha	EC$_{25}$ > 2.28 kg/ha NOEC = 2.28 kg/ha	—

[a] Atkins et al. (1981) for bees and the USEPA classification for others, where applicable

[b] Classification by Hassan et al. (1994) for laboratory tests conducted with inert substrates: <30% harmless; 30–79% slightly harmful; 80–99% moderately harmful; >99% harmful

[c] Atkins et al. (1981) classification

M=mortality; B=beneficial capacity; F=fecundity; E=egg number; W=weight loss; R=reproduction

Table 9 Effects of famoxadone on aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Freshwater species				
Daphnia magna	Acute	Famoxadone (97.7%)	EC$_{50}$ = 11.8 μg a.i./L LC$_{50}$ = 13.0 μg a.i./L NOEC = 3.5 μg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.4%)	NOEC = 0.085 μg a.i./L (Y) LOEC = 0.29 μg a.i./L	—
	Acute	IN-JS940 (98%)	EC$_{50}$ > 9600 μg/L NOEC = 9600 μg/L (M)	At most slightly toxic
Midge *Chironomus riparius*	Chronic	Famoxadone (96.9%)	EC$_{50}$ = 410 μg a.i./L NOEC = 10 μg a.i./L (R)	Highly toxic

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Birds				
Bobwhite quail	Acute Oral	Famoxadone (97.4%)	LD_{50} > 2250 mg a.i./kg bw NOEL = 2250 mg a.i./kg bw (M)	Practically non-toxic
		DPX-KX007-5 WG (22.7% famoxadone, 30.4% cymoxanil) 2250 mg formulation/kg	LD_{50} > 2250 mg/kg bw NOEL = 292 mg/kg bw (W)	Practically non-toxic
	Dietary	Famoxadone (97.4%)	LC_{50} > 5620 mg a.i./kg diet NOEL = 5620 mg a.i./kg diet (M)	Practically non-toxic
	Reproduction	Famoxadone (97.4%)	NOEC = 46 mg a.i./kg diet (M, R) LOEC = 252 mg a.i./kg diet	—
Mallard duck	Dietary	Famoxadone (97.4%)	LC_{50} > 5620 mg a.i./kg diet NOEL = 5620 mg a.i./kg diet (M)	Practically non-toxic
	Reproduction	Famoxadone (97.4%)	NOEC = 46 mg a.i./kg diet (M,R) LOEC = 252 mg a.i./kg diet	—
Mammals				
Rat	Acute	Famoxadone	LD_{50} = 3100 mg/kg bw	Low
		Tanos 50DF	LD_{50} = 1311 mg EP/kg bw	Moderate
	Dietary	Famoxadone	NOAEL: 3.34 mg/kg bw/d (male) 4.24 mg/kg bw/d (female)	—
	Dermal	Tanos 50DF	LD_{50} > 5000 mg EP/kg bw	Low
	Inhalation	Famoxadone	LC_{50} > 5.3 mg/L	Low
		Tanos 50DF	LC_{50} > 5.1 mg EP/L	Low
	Oncogenicity	Famoxadone	NOAEL: 8.4 mg/kg bw/d (male) 2.2 mg/kg bw/d (female)	—
	2-Generation Reproduction	Famoxadone	NOAEL: 11.3 mg/kg bw/d (male) 14.2 mg/kg bw/d (female)	—
	Development	Famoxadone	NOAEL: 250 mg/kg bw/d	—

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**[a]
Mouse	Dietary	Famoxadone	NOAEL: 62.4 mg/kg bw/d (male) 79.9 mg/kg bw/d (female)	—
	Oncogenicity	Famoxadone	NOAEL: 96 mg/kg bw/d (male) 130 mg/kg bw/d (female)	—
Rabbit	Dermal	Famoxadone	$LD_{50} > 2000$ mg/kg	Low
	Development	Famoxadone	NOAEL: 350 mg/kg bw/d	—
Dog	Dietary	Famoxadone	NOAEL: 1.3 mg/kg bw/d (male) NA (female)	—
Monkey	Oncogenicity	Famoxadone	NOAEL: 100 mg/kg bw/d	
Vascular plants				
Vascular plant	Seedling emergence	DPX-JE874 10EC (9.2% famoxadone) 2.28 kg formulation/ha	$EC_{25} > 2.28$ kg/ha NOEC = 2.28 kg/ha	—
	Vegetative vigour	DPX-JE874 10EC (9.2% famoxadone) 2.28 kg formulation/ha	$EC_{25} > 2.28$ kg/ha NOEC = 2.28 kg/ha	—

[a] Atkins et al. (1981) for bees and the USEPA classification for others, where applicable

[b] Classification by Hassan et al. (1994) for laboratory tests conducted with inert substrates: <30% harmless; 30–79% slightly harmful; 80–99% moderately harmful; >99% harmful

[c] Atkins et al. (1981) classification

M=mortality; B=beneficial capacity; F=fecundity; E=egg number; W=weight loss; R=reproduction

Table 9 Effects of famoxadone on aquatic organisms

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**[a]
Freshwater species				
Daphnia magna	Acute	Famoxadone (97.7%)	$EC_{50} = 11.8$ μg a.i./L $LC_{50} = 13.0$ μg a.i./L NOEC = 3.5 μg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.4%)	NOEC = 0.085 μg a.i./L (Y) LOEC = 0.29 μg a.i./L	—
	Acute	IN-JS940 (98%)	$EC_{50} > 9600$ μg/L NOEC = 9600 μg/L (M)	At most slightly toxic
Midge *Chironomus riparius*	Chronic	Famoxadone (96.9%)	$EC_{50} = 410$ μg a.i./L NOEC = 10 μg a.i./L (R)	Highly toxic

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**[a]
Rainbow trout	Acute	Famoxadone (97.7%)	LC_{50} = 12 μg a.i./L NOEC = 5.2 μg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.4%)	NOEC = 1.4 μg a.i./L (A,L) LOEC = 4.1 μg a.i./L	—
	Acute	IN-JS940 (95%)	LC_{50} > 9000 μg/L NOEC = 9000 μg/L (M)	At most slightly toxic
Bluegill sunfish	Acute	Famoxadone (97.7%)	LC50 = 13 μg a.i./L NOEC = 9.3 μg a.i./L (M)	Very highly toxic
Freshwater alga	Chronic—*S. capricornutum*	Famoxadone (97.4%)	EC_{50} = 23 μg a.i./L NOEC = 3.9 g a.i./L (B)	
	Chronic—*A. flos-aquae*	Famoxadone (97.8%)	EC_{50} >84.3 μg a.i./L NOEC = 42.6 μg a.i./L (D,G)	
Vascular plant	*Lemna gibba*	Famoxadone (97.8%)	NOEC = 81 mg a.i./L (B,D)	
Marine species				
Crustacean —shrimp *Mysidopsis bahia*	Acute	Famoxadone (97.4%)	LC_{50} = 3.9 μg a.i./L NOEC = 2.2 μg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.8%)	EC_{50} = 2.98 μg a.i./L NOEC = 0.83 μg a.i./L (M,R) LOEC = 1.72 μg a.i./L	—
Mollusk shell deposition	Acute	Famoxadone (97.8%)	EC_{50} = 1.41 μg a.i./L NOEC < 1.1 μg a.i./L (S)	Very highly toxic
Marine alga	Acute—*Skeletonema costatum*	Famoxadone (97.8%)	EC_{50} = 41.5 μg a.i./L NOEC = 9.09 μg a.i./L (D)	
Sheepshead minnow	Acute	Famoxadone (97.4%)	LC_{50} = 49.4 μg a.i./L NOEC = 27.7 μg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.8%)	NOEC = 5.58 μg a.i./L (M,Y) LOEC = 11.2 μg a.i./L	—

[a] USEPA classification, where applicable

M=mortality; A=abnormalities; L=length; Y=young produced or hatch survival; R=reproductive development; B=biomass; D=cell or frond density; G=growth rate; S=shell deposition

Table 10 Risk of famoxadone to terrestrial organisms

Organism	Exposure	Endpoint value	EEC	MOS	Risk
Invertebrates					
Earthworm	Acute	NOEC = 62.5 mg a.i./kg soil	0.37 mg a.i./kg soil	169	Negligible
Birds					
Bobwhite quail	Acute	NOEL = 2250 mg a.i./kg bw	220.6 mg a.i./kg	10	Negligible
	Dietary	NOEL = 5620 mg a.i./kg diet	220.6 mg a.i./kg	26	Negligible
	Reproduction	NOEC = 46 mg a.i./kg diet	220.6 mg a.i./kg	0.21	Moderate
Mallard duck	Dietary	NOEL = 5620 mg a.i./kg diet	42.6 mg a.i./kg	132	Negligible
	Reproduction	NOEC = 46 mg a.i./kg diet	42.6 mg a.i./kg	1.1	Moderate
Mammals					
Rat	Acute	NOEC = 310 mg a.i./kg diet	635.7 mg a.i./kg	0.5	Moderate
	Dietary	NOAEL = 50 mg a.i./kg diet	635.7 mg a.i./kg	0.08	High
	Reproduction	NOAEL = 200 mg a.i./kg diet	635.7 mg a.i./kg	0.31	Moderate
Mouse	Dietary	NOAEL = 350 mg a.i./kg diet	631.8 mg a.i./kg	0.55	Moderate
Vascular plants					
Vascular plant	Seedling emergence	EC_{25} > 2.28 kg/ha	0.56–0.84 kg/ha	>1	Low
	Vegetative vigour	EC_{25} > 2.28 kg/ha	0.56–0.84 kg/ha	>1	Low

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Rainbow trout	Acute	Famoxadone (97.7%)	LC$_{50}$ = 12 µg a.i./L NOEC = 5.2 µg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.4%)	NOEC = 1.4 µg a.i./L (A,L) LOEC = 4.1 µg a.i./L	—
	Acute	IN-JS940 (95%)	LC$_{50}$ > 9000 µg/L NOEC = 9000 µg/L (M)	At most slightly toxic
Bluegill sunfish	Acute	Famoxadone (97.7%)	LC50 = 13 µg a.i./L NOEC = 9.3 µg a.i./L (M)	Very highly toxic
Freshwater alga	Chronic—*S. capricornutum*	Famoxadone (97.4%)	EC$_{50}$ = 23 µg a.i./L NOEC = 3.9 g a.i./L (B)	
	Chronic—*A. flos-aquae*	Famoxadone (97.8%)	EC$_{50}$ >84.3 µg a.i./L NOEC = 42.6 µg a.i./L (D,G)	
Vascular plant	*Lemna gibba*	Famoxadone (97.8%)	NOEC = 81 mg a.i./L (B,D)	
Marine species				
Crustacean —shrimp *Mysidopsis bahia*	Acute	Famoxadone (97.4%)	LC$_{50}$ = 3.9 µg a.i./L NOEC = 2.2 µg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.8%)	EC$_{50}$ = 2.98 µg a.i./L NOEC = 0.83 µg a.i./L (M,R) LOEC = 1.72 µg a.i./L	—
Mollusk shell deposition	Acute	Famoxadone (97.8%)	EC$_{50}$ = 1.41 µg a.i./L NOEC < 1.1 µg a.i./L (S)	Very highly toxic
Marine alga	Acute—*Skeletonema costatum*	Famoxadone (97.8%)	EC$_{50}$ = 41.5 µg a.i./L NOEC = 9.09 µg a.i./L (D)	
Sheepshead minnow	Acute	Famoxadone (97.4%)	LC$_{50}$ = 49.4 µg a.i./L NOEC = 27.7 µg a.i./L (M)	Very highly toxic
	Chronic	Famoxadone (97.8%)	NOEC = 5.58 µg a.i./L (M,Y) LOEC = 11.2 µg a.i./L	—

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M=mortality; A=abnormalities; L=length; Y=young produced or hatch survival; R=reproductive development; B=biomass; D=cell or frond density; G=growth rate; S=shell deposition

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	Dietary	NOEL = 5620 mg a.i./kg diet	220.6 mg a.i./kg	26	Negligible
	Reproduction	NOEC = 46 mg a.i./kg diet	220.6 mg a.i./kg	0.21	Moderate
Mallard duck	Dietary	NOEL = 5620 mg a.i./kg diet	42.6 mg a.i./kg	132	Negligible
	Reproduction	NOEC = 46 mg a.i./kg diet	42.6 mg a.i./kg	1.1	Moderate
Mammals					
Rat	Acute	NOEC = 310 mg a.i./kg diet	635.7 mg a.i./kg	0.5	Moderate
	Dietary	NOAEL = 50 mg a.i./kg diet	635.7 mg a.i./kg	0.08	High
	Reproduction	NOAEL = 200 mg a.i./kg diet	635.7 mg a.i./kg	0.31	Moderate
Mouse	Dietary	NOAEL = 350 mg a.i./kg diet	631.8 mg a.i./kg	0.55	Moderate
Vascular plants					
Vascular plant	Seedling emergence	EC_{25} > 2.28 kg/ha	0.56–0.84 kg/ha	>1	Low
	Vegetative vigour	EC_{25} > 2.28 kg/ha	0.56–0.84 kg/ha	>1	Low

Table 11 Risk of famoxadone to aquatic organisms

Organism	Exposure	Endpoint value	EEC	MOS	Risk
Freshwater species					
Daphnia magna	Acute	NOEC = 3.5 µg a.i./L	77 µg a.i./L	0.05	High
	Chronic	NOEC = 0.085 µg a.i./L	77 µg a.i./L	0.001	Very high
Chironomus riparius	Chronic	NOEC = 10 µg a.i./L	77 µg a.i./L	0.13	Moderate
Rainbow trout	Acute	NOEC = 5.2 µg a.i./L	77 µg a.i./L	0.07	High
	Chronic	NOEL = 1.4 µg a.i./L	77 µg a.i./L	0.02	High
Bluegill sunfish	Acute	NOEC = 9.3 µg a.i./L	77 µg a.i./L	0.12	Moderate
Freshwater algae	Acute	NOEC = 3.9 µg a.i./L	77 µg a.i./L	0.05	High
Vascular plant	Dissolved	NOEC = 81 µg a.i./L	77 µg a.i./L	1.05	Low
Marine species					
Crustacean—mysid shrimp	Acute	NOEC = 2.2 µg a.i./L	77 µg a.i./L	0.03	High
	Chronic	NOEC = 0.83 µg a.i./L	77 µg a.i./L	0.01	High
Mollusk—oyster	Acute	NOEC < 1.1 µg a.i./L	77 µg a.i./L	0.01	High
Sheepshead minnow	Acute	NOEC = 27.7 µg a.i./L	77 µg a.i./L	0.36	Moderate
	Chronic	NOEC = 5.58 µg a.i./L	77 µg a.i./L	0.07	High
Marine algae	Acute	NOEC = 9.09 g a.i./L	77 µg a.i./L	0.12	Moderate

Table 11 Risk of famoxadone to aquatic organisms

Organism	Exposure	Endpoint value	EEC	MOS	Risk
Freshwater species					
Daphnia magna	Acute	NOEC = 3.5 µg a.i./L	77 µg a.i./L	0.05	High
	Chronic	NOEC = 0.085 µg a.i./L	77 µg a.i./L	0.001	Very high
Chironomus riparius	Chronic	NOEC = 10 µg a.i./L	77 µg a.i./L	0.13	Moderate
Rainbow trout	Acute	NOEC = 5.2 µg a.i./L	77 µg a.i./L	0.07	High
	Chronic	NOEL = 1.4 µg a.i./L	77 µg a.i./L	0.02	High
Bluegill sunfish	Acute	NOEC = 9.3 µg a.i./L	77 µg a.i./L	0.12	Moderate
Freshwater algae	Acute	NOEC = 3.9 µg a.i./L	77 µg a.i./L	0.05	High
Vascular plant	Dissolved	NOEC = 81 µg a.i./L	77 µg a.i./L	1.05	Low
Marine species					
Crustacean—mysid shrimp	Acute	NOEC = 2.2 µg a.i./L	77 µg a.i./L	0.03	High
	Chronic	NOEC = 0.83 µg a.i./L	77 µg a.i./L	0.01	High
Mollusk—oyster	Acute	NOEC < 1.1 µg a.i./L	77 µg a.i./L	0.01	High
Sheepshead minnow	Acute	NOEC = 27.7 µg a.i./L	77 µg a.i./L	0.36	Moderate
	Chronic	NOEC = 5.58 µg a.i./L	77 µg a.i./L	0.07	High
Marine algae	Acute	NOEC = 9.09 g a.i./L	77 µg a.i./L	0.12	Moderate